IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.: 6,208,749 | Customer No. 051414

Inventors: Gutkowicz-Krusin et al. | Assignee: MELA Sciences, Inc.

Issued: March 27, 2001 | Approved Product: MelaFind® System

Title: SYSTEMS AND METHODS FOR THE MULTISPECTRAL IMAGING AND CHARACTERIZATION OF SKIN TISSUE

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Signature: Deanna Bridges

Name: DEANNA BRIDGES

Date: December 19, 2011

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Mail Stop: **Patent Ext.**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Mail Stop: **Patent Ext.**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

MELA Sciences, Inc. hereby applies for extension of the term of U.S. Patent No. 6,208,749 to Gutkowicz-Krusin et al. (hereinafter "the '749 Patent").

Applicant MELA Sciences, Inc. is the owner of the '749 Patent by virtue of an assignment from all of the inventors to Electro-Optical Sciences, Inc. (recorded on April 24, 1998 at Reel 009137, Frame 0244), and a subsequent name change of Electro-Optical Sciences, Inc. to MELA Sciences, Inc. (recorded on May 7, 2010 at Reel 024351, Frame 0849). Documentation of the foregoing may be found in **Exhibit A** and **Exhibit B**, respectively.

MELA Sciences, Inc., acting through its duly authorized attorney, hereby submits this application for extension of patent term in accordance with 35 U.S.C. §156 and 37 C.F.R. §§1.710 – 1.785. The original and four copies of this application are being submitted. If any further information is required, please advise the undersigned.

I. ELIGIBILITY FOR PATENT TERM EXTENSION

Applicant believes the '749 Patent is eligible for patent term extension in accordance with 35 U.S.C. §156(a)(1)-(5) and 37 C.F.R. §1.720(a)-(h), as follows:

A. The '749 Patent claims a product and a method of using or manufacturing the product as defined in 37 C.F.R. § 1.710, namely the MelaFind® system and methods for its use (37 C.F.R. §1.710(b)(3) and §1.720(a)).

B. The term of the '749 Patent has never been previously extended, has not been extended under subsection (e)(1) of 35 U.S.C. §156, and has not been issued extensions under 37 C.F.R. §§ 1.701, 1.760, or 1.790 (35 U.S.C. §156(a)(2) and 37 C.F.R. §1.720(b)).

C. This application for extension of the '749 Patent is submitted in compliance with 35 U.S.C. §156(d)(1)-(4) and 37 C.F.R. §1.740 by the patent owner, MELA Sciences, Inc., through its undersigned representative (35 U.S.C. §156(a)(3) and 37 C.F.R. §1.720(c)).

D. The product claimed in the '749 Patent, namely the MelaFind® system, has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use (35 U.S.C. §156(a)(4) and 37 C.F.R. §1.720(d)).

E. The product claimed in the '749 Patent has received permission for commercial marketing or use after such regulatory review period, and such permission is the first received permission for commercial marketing or use under the provision of law under which such regulatory review occurred (35 U.S.C. §156(a)(5)(A) and 37 C.F.R. §1.720(e)(1)).

F. This application for extension of the '749 Patent is being submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred (37 C.F.R. §1.720(f)). The date the product first received permission is November 1, 2011. As the sixty-day period ends on Saturday, December 31st, and Monday, January 2nd is New Year's Day observed, the sixty-day period ends on the next business day, i.e., January 3, 2012 (MPEP §2753).

G. The term of the '749 Patent, including any interim extension issued pursuant to 37 C.F.R. §1.790, has not expired before the submission of this application in compliance with 37 CFR §1.741 (35 U.S.C. §156(a)(1), 37 C.F.R. §1.720(g)).

H. No other patent term has been extended for the same regulatory review period for this product (37 C.F.R. §1.720(h)).

II. FORMAL REQUIREMENTS FOR APPLICATION

A. COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS (37 C.F.R. §1.740(a)(1))

The approved product is a device for characterizing the condition of a region of interest of skin, namely, the differentiation of pigmented skin lesions that are positive for melanoma

from those that are negative for the disease. The product is marketed under the trademarked name "MelaFind®." The MelaFind system is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. The MelaFind system is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy; however, the device should not be used to confirm a clinical diagnosis of melanoma.

The MelaFind system, depicted below in Figure 1, includes a handheld device for image capture, a base computer connected to the hand-held device via a universal serial bus cable, a touch-screen display monitor, and removable media. A high-level flowchart of the functionality of the MelaFind system is provided in Figure 3. The handheld imaging device, shown below in Figure 2 and flowcharted in Figure 4, is used to capture lesion images and includes an illuminator that provides light of ten specific wavelengths, a lens system that creates images of the light scattered back from the lesions, and a CMOS photo sensor. The base computer contains a processor that executes computer software having automatic image analysis algorithms. These algorithms include image calibration for noise and artifact reduction, image quality control for determining whether a lesion should be reimaged, lesion segmentation for identifying portions of the image associated with a lesion, feature extraction for computing parameters characterizing lesions, and lesion classification for evaluating whether a lesion exhibits the characteristics of melanoma. The sequence of these algorithms is further illustrated below in Figure 5. The touch-screen display allows the operator to examine the visual output of the MelaFind system and otherwise interact with the device.

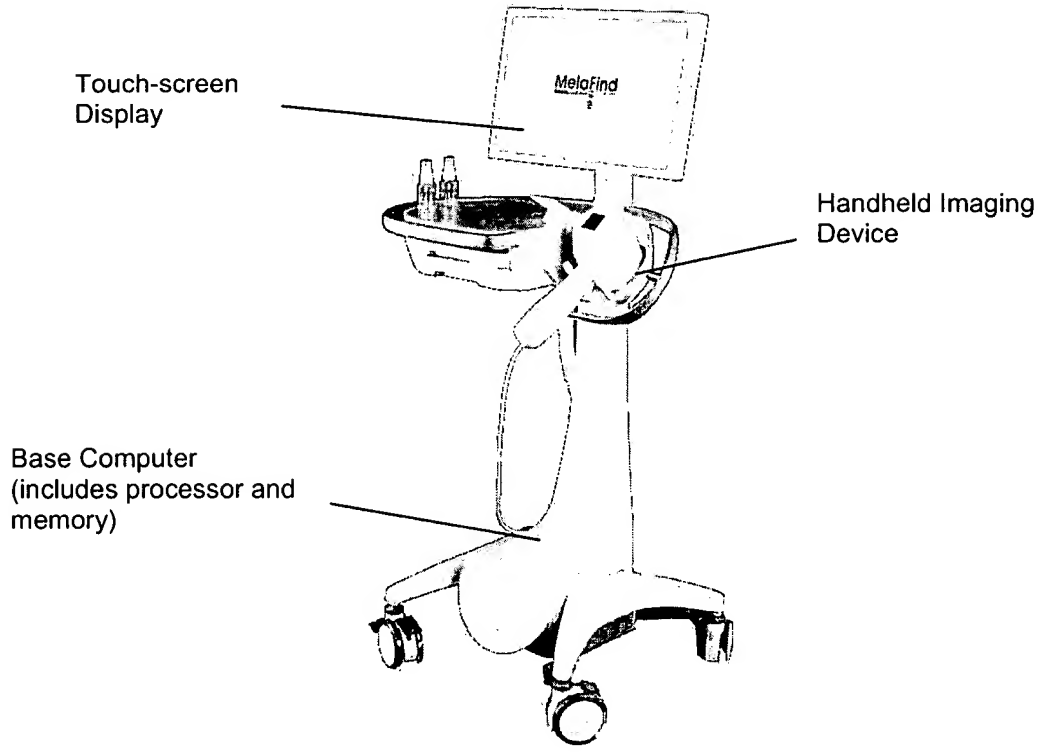

Figure 1 – MelaFind® System

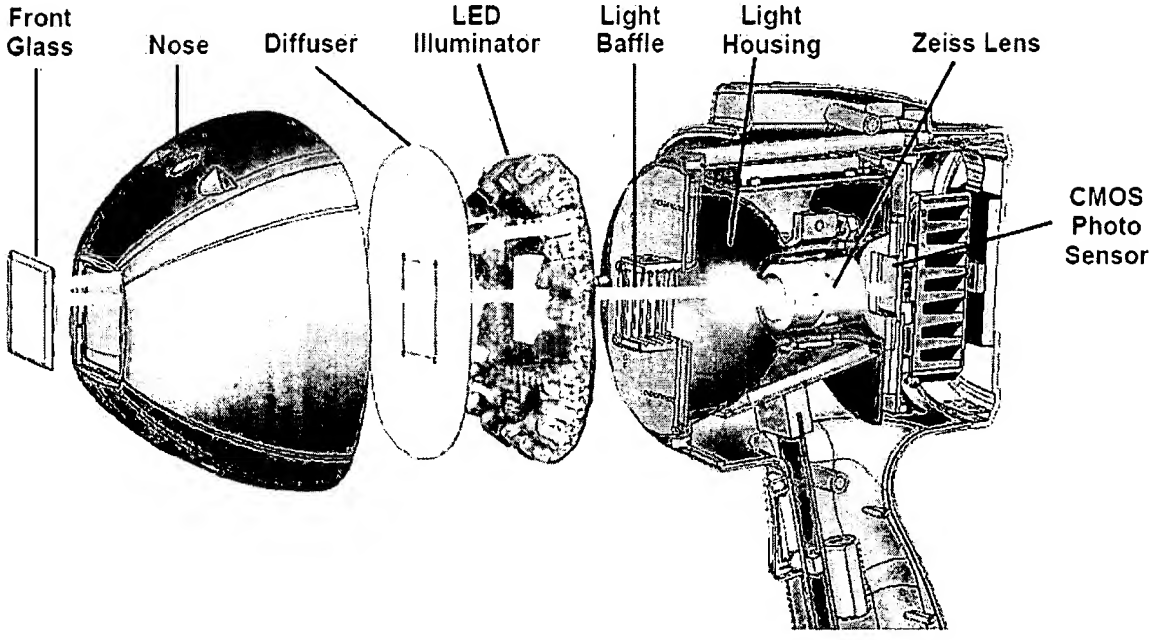

Figure 2 - Handheld Imaging Device

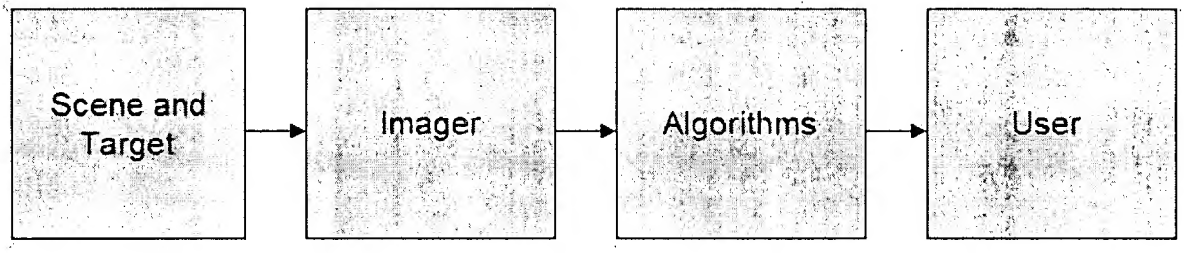

Figure 3 - MelaFind System High-Level Functionality Flowchart

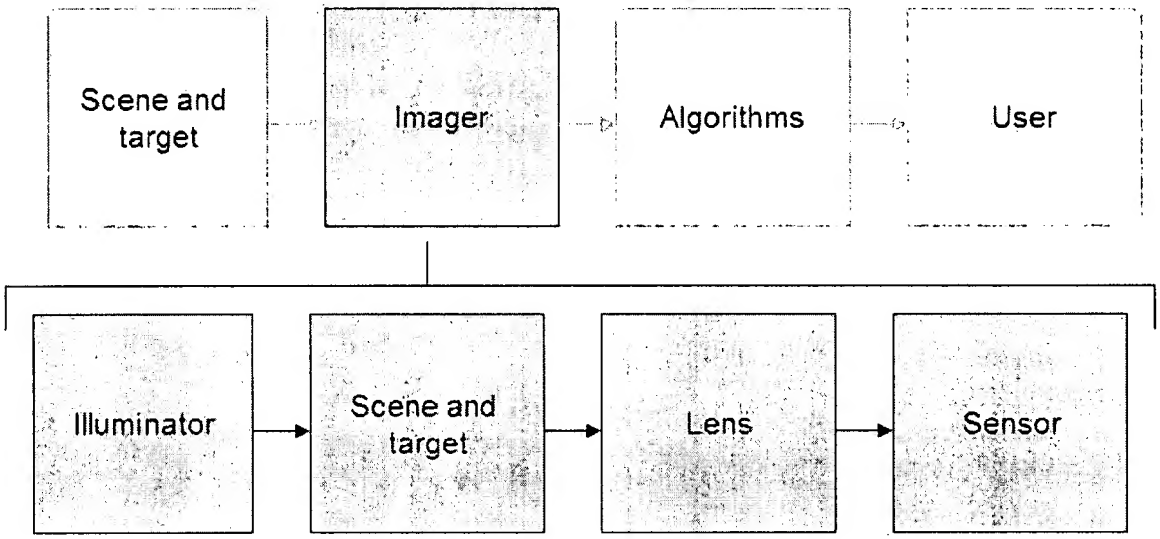

Figure 4 - Imager Flowchart

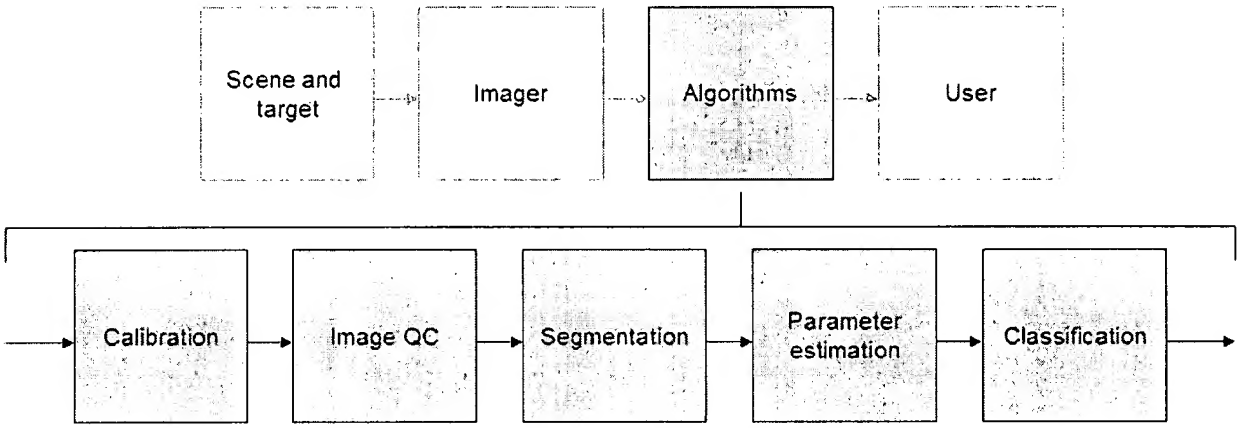

Figure 5 - Algorithms Flowchart

B. COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED (37 C.F.R. §1.740(a)(2))

The approved device, the MelaFind system, was subject to regulatory review under Section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360e) as a medical device, and was subject to a binding protocol agreement under Section 520(g)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360j(g)(7)). The approved device was clinically tested as a not significant risk device under 21 C.F.R. §812.2(b) in accordance with Section 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360j).

The regulatory review was conducted by the Center for Devices and Radiological Health (CDRH) of the United States Food and Drug Administration (FDA), including CDRH's Office of Device Evaluation – Division of Surgical, Orthopedic and Restorative Devices.

C. IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED (37 C.F.R. §1.740(a)(3))

The product received permission for commercial marketing or use under Section 515(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360e(d)) on November 1, 2011.

D. STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO § 1.720(F) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED (37 C.F.R. §1.740(a)(5))

The present application for extension is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application may be submitted is December 31, 2011. However, since December 31st is a Saturday, and Monday, January 2nd is New Year's Day observed, the last day on which this application may be submitted is January 3, 2012.

E. COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION (37 C.F.R. §1.740(a)(6))

The patent for which an extension is being sought is U.S. Patent No. 6,208,749 B1, which issued March 27, 2001. The inventors are Dina Gutkowicz-Krusin, Marek Elbaum, Michael Greenebaum, and Adam Jacobs. The '749 patent issued on a continued prosecution application filed under 37 C.F.R. §1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. §154(a)(2). The '749 Patent is not subject to any terminal disclaimer. The term of the '749 patent was adjusted under 35 U.S.C. §154(b) by zero (0) days. The '749 patent is therefore set to expire twenty years from its filing date of February 27, 1998, i.e., February 27, 2018, subject to payment of maintenance fees.

F. COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS (37 C.F.R. §1.740(a)(7))

A copy of the entire '749 Patent is attached as **Exhibit C**.

G. COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT (37 C.F.R. §1.740(a)(8))

No disclaimer or reexamination certificate has been filed or issued in the '749 Patent. Copies of the applicable maintenance fee payment receipts from September 9, 2004 and April 14, 2008 are attached as **Exhibit D**. The twelfth-year maintenance fee window will not open until March 27, 2012. No certificate of correction has been issued for the '749 Patent; however, a Request for Certificate of Correction has been filed concurrently with this application to correct a minor typographical error in independent method claim 17. A copy of the request can be found in **Exhibit E**.

H. STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT AND THE METHOD OF USING THE APPROVED PRODUCT (37 C.F.R. §1.740(a)(9))

The '749 patent claims the approved MelaFind product and a method of using the approved MelaFind product. Applicant asserts that at least claims 45-68 read on the approved product, and that at least claims 1-9, 11, 15, 17-20, 22, 26-29, 32-39, 40 and 43 read on a method of using the approved product.

Independent system claim 45 reads on the approved product, as follows:

Table 1 - Chart for Claim 45 of the '749 Patent

Claim 45 of the '749 Patent	Corresponding Features in the MelaFind® System
A system for characterizing the condition of a region of interest of skin, comprising:	The MelaFind® system, shown in Figure 1, is a multi-spectral, non-invasive computer-vision system that classifies the image of a pigmented skin lesion based upon degree of disorganization: MelaFind positive (high degree of disorganization) or MelaFind negative (low degree of disorganization). The MelaFind system is intended for use on clinically atypical pigmented skin lesions with one or more clinical or historical characteristics of melanoma and is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy.
a source of illumination of light in at least three spectral bands;	Figure 2 illustrates the MelaFind handheld imager, that includes an LED illuminator emitting light in ten spectral bands, from 430 to 950 nm.

Claim 45 of the '749 Patent	Corresponding Features in the MelaFind® System
a camera for acquiring digital images of the region of interest based on the light re-emitted from the illuminated region of interest at each of the spectral bands, the digital image comprising digital signals whose values are a function of the condition of the region of interest;	Figure 2 shows the camera within the MelaFind handheld imager, including a 9-element Zeiss lens and a CMOS photo sensor. The camera is used for acquiring digital images of a region of interest that includes an atypical pigmented skin lesion based on the light re-emitted from the illuminated region of interest in each of ten spectral bands. The values of intensity in these images are a function of the condition (i.e., the degree of disorganization) in the region of interest.
memory for storing the digital images provided by the camera;	Figure 1 shows that the MelaFind system's base computer incorporates memory (electronic storage media) for storing the digital images provided by the camera.
a digital processor programmed to perform the steps of:	Figure 1 shows the base computer having a digital processor. The processor is programmed to perform the analysis of multi-spectral images.
segmenting the digital images stored in memory by generating a single segmentation mask, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the at least three spectral bands;	Figure 5 illustrates the algorithmic functions performed by the MelaFind system. Following image calibration and quality checking, the digital processor executes programming that segments images to identify an atypical pigmented skin lesion in the field of view ("Segmentation"). A single segmentation mask is created for all ten spectral bands; this is the mask having the largest area of the segmentation masks generated in each spectral band.
estimating at least one value for each digital image at each spectral band which is a function of the texture of the portion of the region of interest determined by the segmentation mask;	Figure 5 further shows that the MelaFind system estimates values in each spectral band ("Parameter Estimation") as part of the sequence of executed algorithms. The values are functions of the texture of the region of interest determined by the segmentation mask.
characterizing the condition of the skin based on the estimated values; and	As shown in Figure 5, the MelaFind processor characterizes the condition of the skin as having a high or low degree of disorganization based on estimated values (75 parameters) in all ten spectral bands ("Classification").

Claim 45 of the '749 Patent	Corresponding Features in the MelaFind® System
outputting the characterization of the region of interest.	As depicted in Figure 3, following the targeting, imaging, and algorithm steps, the MelaFind system outputs the characterization of the region of interest to the user: MelaFind positive (high degree of disorganization) or MelaFind negative (low degree of disorganization).

Independent method claim 17 reads on a method for using the approved product, as follows:

Table 2 - Chart for Claim 17 of the '749 Patent

Claim 17 of the '749 Patent	Corresponding Features in the MelaFind® System
A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:	The MelaFind® system, shown in Figure 1, is a multi-spectral, non-invasive computer-vision system that classifies the image of a pigmented skin lesion based upon degree of disorganization: MelaFind positive (high degree of disorganization) or MelaFind negative (low degree of disorganization). The MelaFind system is intended for use on clinically atypical pigmented skin lesions with one or more clinical or historical characteristics of melanoma and is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy.

Claim 17 of the '749 Patent	Corresponding Features in the MelaFind® System
illuminating a portion of the skin including the region of interest by light in at least three spectral bands;	Figure 2 illustrates the MelaFind handheld imager, that includes an LED illuminator used to illuminate a portion of skin by emitting light in ten spectral bands, from 430 to 950 nm. Figure 4 shows the imaging process, starting with the illumination of the region of interest.
digitally imaging the portion of the skin including the region of interest at the at least tree[1] spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and	Figure 2 shows a camera within the MelaFind handheld imager, including a 9-element Zeiss lens and a CMOS photo sensor. The camera is used for digitally imaging a region of interest that includes an atypical pigmented skin lesion based on the light re-emitted from the illuminated region of interest in each of ten spectral bands. The values of intensity in these images are a function of the condition (i.e., the degree of disorganization) in the region of interest. Figure 4 shows a flowchart of the imaging process, in which the lens and sensor facilitate the digital imaging of the illuminated region of interest.
providing the digital images to a processor, wherein the processor:	Figure 1 shows the base computer having a digital processor. The processor is programmed to perform the analysis of multi-spectral images.
segments the digital images by generating a single segmentation mask defining the boundary of the region of interest for each image, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the last least three spectral bands;	Figure 5 illustrates the algorithmic functions performed by the MelaFind system. Following image calibration and quality checking, the digital processor executes programming that segments images to identify an atypical pigmented skin lesion in the field of view ("Segmentation"). A single segmentation mask is created for all ten spectral bands; this is the mask having the largest area of the segmentation masks generated in each spectral band.

[1] Applicant recognizes that a typographical error exists in this claim 17. The correct term should be "three." Applicant has submitted a Request for Certificate of Correction concurrently with this application, a copy of which is provided in **Exhibit E**.

Claim 17 of the '749 Patent	Corresponding Features in the MelaFind® System
computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the region of interest determined by the segmentation mask;	Figure 5 further shows that the MelaFind system estimates values in each spectral band ("Parameter Estimation") as part of the sequence of executed algorithms. The values are functions of the texture of the region of interest determined by the segmentation mask.
characterizes the condition of the region of interest of the skin based on the estimated values; and	As shown in Figure 5, the MelaFind processor characterizes the condition of the skin as having a high or low degree of disorganization based on estimated values (75 parameters) in all ten spectral bands ("Classification").
outputs the characterization of the condition of the region of interest of the skin.	As depicted in Figure 3, following the targeting, imaging, and algorithm steps, the MelaFind system outputs the characterization of the region of interest to the user: MelaFind positive (high degree of disorganization) or MelaFind negative (low degree of disorganization).

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I. RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(G) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD (37 C.F.R. §1.740(a)(10))

The '749 Patent claims a medical product that was subject to an approved investigational device exemption (IDE) as a not significant risk (NSR) device by the FDA, pursuant to 21 C.F.R. §812.2(b); therefore, 37 C.F. R. § 1.740(a)(10)(v) applies.

(A) The effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device, if no IDE was submitted, and any available substantiation of that date:

The effective date on which the applicant obtained approval of a not significant risk IDE to conduct clinical investigations, i.e., the Institutional Review Board (IRB) approval date, was May 2, 2001 (see **Exhibit F** for the Certificate of Approval). Applicant believes the effective date of the first clinical investigation involving the device is the IRB approval date for the purposes of this application. See 21 C.F.R. §60.22(c)(1)(i) and (ii).

(B) The date on which the application for product approval or notice of completion of a product development protocol under Section 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application:

The application for product approval under Section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and filed by the FDA on June 9, 2009. The letter from the FDA Center for Devices and Radiological Health provided in **Exhibit G** substantiates this date. The PMA number was P090012.

(C) The date on which the application was approved or the protocol declared to be completed:

The PMA was approved on November 1, 2011. The letter from the FDA substantiating that approval date is provided in **Exhibit H**.

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J. BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES (37 C.F.R. §1.740(a)(11))

Attached as **Exhibit I** is a table listing significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates such activities occurred. Further details regarding the marketing applicant's activities during the regulatory review period may be provided upon request.

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K. STATEMENT THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED (37 C.F.R. §1.740(a)(12))

In the opinion of the Applicant, U.S. Patent No. 6,208,749 is eligible for patent term extension, under 35 U.S.C. § 156 because:

(i) one or more of the claims of U.S. Patent No. 6,208,749 claim the approved product (the MelaFind system);

(ii) the term of U.S. Patent No. 6,208,749 has not been extended on the basis of 35 U.S.C. § 156 before the submission of the instant application;

(iii) the term of no other U.S. Patent has been extended under 35 U.S.C. § 156 on the basis of the regulatory review process associated with the approved product (the MelaFind system);

(iv) there is an eligible period of regulatory review by which the patent may be extended pursuant to 35 U.S.C. § 156;

(v) the present application has been submitted within the 60-day period following the approval date of the approved product, pursuant to 35 U.S.C. § 156(c);

(vi) the applicant before the FDA is the owner of U.S. Patent No. 6,208,749 by virtue of the assignment documents attached as **Exhibit A** and **Exhibit B**; and

(vii) the application submitted here otherwise complies with all requirements of 35 U.S.C. § 156 and all applicable rules and procedures.

The period of extension of the term of U.S. Patent No. 6,208,749 requested by Applicant is 5 (five) years, such that the patent would expire on February 27, 2023. The length of the extension was determined according to 35 U.S.C. §§156(c), (g)(3), (g)(6), and 37 C.F.R. §1.777, as shown below.

1) The number of days in the period beginning on the date a clinical investigation on humans involving the device was begun and ending on the date an application was initially submitted with respect to the device under section 515 of the Federal Food, Drug, and Cosmetic Act is **2960 days.**

2) The number of days in the period beginning on the date the application was initially submitted with respect to the device under section 515 of the Federal Food, Drug, and Cosmetic Act, and ending on the date such application was approved under such Act or the period beginning on the date a notice of completion of a product development protocol was initially submitted under section 515(f)(5) of the Act and ending on the date the protocol was declared completed under section 515(f)(6) of the Act is **875 days.**

3) The dates pertaining to nos. 1 and 2 above, so that it can be determined how many days occurred prior to issuance of the patent, are as follows. The IRB approval date was May 2, 2001. The PMA submission date was June 9, 2009. U.S. Patent No. 6,208,749 issued on March 27, 2001, whereby 0 days should be subtracted based on activities on or before the patent issuance date.

Applicant submits that it has acted with due diligence throughout the clinical investigation period and the pre-market approval period, whereby 0 days should be subtracted from the regulatory review period for lack of due diligence.

One half the number of days remaining in the period defined by paragraph (c)(1) of 37 C.F.R. §1.777: **1480 days**

Total relevant period pursuant to 37 C.F.R. §1.777(d)(1): **1480 + 875 = 2355 days.**

4) The expiration date of the patent:

Pursuant to 37 C.F.R. §1.777(d)(5): Adding 5 years to the original expiration of the patent, the new expiration date of the patent appears to be **February 27, 2023**, which is the earlier date, as compared to adding 2355 days to the original expiration date, and is not greater than 14 years from the date of regulatory approval, November 1, 2011.

L. STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE (37 C.F.R. §1.740(a)(13))

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought herein.

M. PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (37 C.F.R. §1.740(a)(14))

Please charge the fee prescribed in 37 C.F.R. §120(j)(1) for a patent term extension application under 35 U.S.C. §156 to Deposit Account No. 07-1700. The Director is authorized to charge the required fees and any underpayment or credit any overpayment to Deposit Account No. 07-1700 for any necessary matter in connection with this application.

N. NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED (37 C.F.R. §1.740(a)(15))

Correspondence in connection with this application shall be directed to:

Christopher W. Stamos
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Respectfully submitted,

Date: 19 December 2011 By: Christopher W. Stamos

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Customer No. 51414

EXHIBIT A

Assignment from Inventors to Electro-Optical Sciences, Inc.

[redacted]

PRD 4/24/98

ASSIGNMENT RECORDING
Patents Only

05-06-1998

[redacted]

100703245

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Commissioner of Patents
Box Assignments
Washington, D.C. 20231

Sir:

Please record the attached original document or copy thereof

1. FROM: Dina Gutkowicz-Krusin, Marek Elbaum, Michael Greenebaum and Adam Jacobs

2. TO: Electro-Optical Sciences, Inc.

ADDRESS: 1 Bridge Street
Irvington, New York 10533

3. conveying by ASSIGNMENT executed on April 5th, 1998.

4. IF ACCOMPANYING THIS TRANSMITTAL, the new application executed on _____, 199_, and/or the following applications and patents:

A. Patent Application No.(s) B. Patent No.(s)

09/032,450

5. Address correspondence to:

BROOKS HAIDT HAFFNER & DELAHUNTY
99 Park Avenue
New York, New York 10016

6. For the one application(s) and/or patent(s) involved

7. the fee (37CFR 3.41) of $40.00 at $40.00 each is enclosed.

8. Should there be any additional fee or an overpayment please charge or credit our Deposit Account No. 02-3976.

9. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: April 21, 1998

05/04/1998 SMITH 00000110 09032450
01 FC:581 40.00 OP

Name: Brandon N. Sklar
Reg. No. 31,667

Total number of pages including cover sheet(s) and document:(two).
EOS-010

Assignment

FOR VALUE RECEIVED Dina Gutkowicz-Krusin, Marek Elbaum, Michael Greenebaum and Adam Jacobs

residing at The United States of America

residing 229 Shadybrook Lane, Princeton, New Jersey 08540, 79 Beechdale Road, Dobbs Ferry, New York 10522, 1177 East 19th Street, Brooklyn, New York 11230 and 212 Baldwin Street, Glen Ridge, New Jersey 07028, respectively,

hereby sell, assign, transfer and convey unto Electro-Optical Sciences, Inc.

a corporation of the State of Delaware

having a place of business at 1 Bridge Street
Irvington, New York 10533

(hereinafter called the "Assignee"), its successors, assigns and legal representatives, the entire right, title and interest, for all countries, in and to certain inventions relating to SYSTEMS AND METHODS FOR THE MULTISPECTRAL IMAGING AND CHARACTERISATION OF SKIN TISSUE

and described in an application for Letters Patent of the United States ~~government~~ filed --- on February 27, 1998, bearing U.S. Patent Application No. 09/032,450

and in and to said application, and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon, and all reissues and extensions thereof, and all applications for Letters Patent which may be filed, and all Letters Patent which may be granted, upon said inventions in any countries foreign to the United States, and all reissues, renewals and extensions thereof; and WE hereby authorize and request the Commissioner of Patents and Trademarks of the United States, and all officials of countries foreign to the United States having authority to so do, to issue all Letters Patent upon said inventions to the Assignee, its successors, assigns or legal representatives or to such nominee as it may designate.

AND WE authorize and empower the said Assignee, its successors, assigns and legal representatives or nominees, to invoke and claim for any application for patent or other form of protection for said inventions filed by it or them, the benefit of the right of priority provided by the International Convention for the Protection of Industrial Property, as amended, or by any convention which may hereinafter be substituted for it, and to invoke and claim such right of priority without further evidence or oral authorization from

AND WE hereby request that a copy of this assignment shall be deemed a full legal and formal equivalent of any assignment, consent to file or like document which may be required in any country for any purpose and more particularly in proof of the right of the said Assignee or nominee to claim the aforesaid benefit of the right of priority provided by the International Convention for the Protection of Industrial Property, as amended, or by any convention which may hereinafter be substituted for it.

AND WE hereby covenant that WE have the full right to convey the entire right, title and interest herein assigned and that WE have not executed and will not execute any agreement in conflict herewith.

AND WE hereby covenant and agree that WE will communicate to said Assignee, its successors, assigns and legal representatives, all facts known to US pertaining to said inventions, and testify in all legal proceedings, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths, and to generally perform all lawful acts necessary or proper to aid said Assignee, its successors, assigns and legal representatives or nominee in obtaining, maintaining and enforcing lawful patent protection for said inventions in any and all countries.

IN TESTIMONY WHEREOF, WE hereunto set OUR hand and seal this 5th day of April, 19 98

Dina Gutkowicz-Krusin ..... L.S.

Marek Elbaum ..... L.S.

Michael Greenebaum ..... L.S.

Adam Jacobs ..... L.S.

---------- ..... L.S.

STATE OF
COUNTY OF } ss.:

On this day of , 19 , before me personally appeared

to me known and known to me to be the individual described in and who executed the foregoing instrument, and who thereupon acknowledged to me that executed the same for the purposes therein stated.

(Seal)

Notary Public
(Notarial Stamp)

EXHIBIT B

Name Change from Electro-Optical Sciences, Inc. to MELA Sciences, Inc.

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF NAME

CONVEYING PARTY DATA

Name	Execution Date
Electro-Optical Sciences, Inc.	04/30/2010

RECEIVING PARTY DATA

Name:	MELA Sciences, Inc.
Street Address:	50 South Buckhout Street
Internal Address:	Suite 1
City:	Irvington
State/Country:	NEW YORK
Postal Code:	10533

PROPERTY NUMBERS Total: 34

Property Type	Number
Patent Number:	5973784
Patent Number:	6081612
Patent Number:	6201880
Patent Number:	6208749
Patent Number:	6282359
Patent Number:	6307957
Patent Number:	6341957
Patent Number:	6563616
Patent Number:	6626558
Patent Number:	6657798
Patent Number:	6672868
Patent Number:	6710947
Patent Number:	6714657
Patent Number:	7102672

OP $1360.00 5973784

Patent Number:	7127094
Patent Number:	D613866
Patent Number:	D613867
Application Number:	11500197
Application Number:	11681345
Application Number:	11761816
Application Number:	12204247
Application Number:	11956918
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Application Number:	61242204
Application Number:	61280386
PCT Number:	US9723953
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PCT Number:	US0775333
PCT Number:	US0855470
PCT Number:	US0866636
PCT Number:	US0875186
PCT Number:	US0886576

CORRESPONDENCE DATA

Fax Number: (914)591-3785

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone: 914 591-3783 Ext 721

Email: greenebaum@eosciences.com

Correspondent Name: Michael Greenebaum, MELA Sciences, Inc.

Address Line 1: 50 South Buckhout Street

Address Line 2: Suite 1

Address Line 4: Irvington, NEW YORK 10533

NAME OF SUBMITTER:	Michael Greenebaum

Total Attachments: 1
source=Page_1_of_Delaware_restated_Certificate_of_Incorporation#page1.tif

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "ELECTRO-OPTICAL SCIENCES, INC.", CHANGING ITS NAME FROM "ELECTRO-OPTICAL SCIENCES, INC." TO "MELA SCIENCES, INC.", FILED IN THIS OFFICE ON THE THIRTIETH DAY OF APRIL, A.D. 2010, AT 1:17 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Jeffrey W Bullock, Secretary of State

2778666 8100

100447059

AUTHENTICATION: 7966229

DATE: 04-30-10

You may verify this certificate online at corp.delaware.gov/authver.shtml

EXHIBIT C

Copy of U.S. Patent No. 6,208,749

US006208749B1

(12) **United States Patent**
Gutkowicz-Krusin et al.

(10) **Patent No.: US 6,208,749 B1**
(45) **Date of Patent: *Mar. 27, 2001**

(54) **SYSTEMS AND METHODS FOR THE MULTISPECTRAL IMAGING AND CHARACTERIZATION OF SKIN TISSUE**

(75) Inventors: **Dina Gutkowicz-Krusin**, Princeton, NJ (US); **Marek Elbaum**, Dobbs Ferry; **Michael Greenebaum**, Brooklyn, both of NY (US); **Adam Jacobs**, Glen Ridge, NJ (US)

(73) Assignee: **Electro-Optical Sciences, Inc.**, Irvington, NY (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/032,450**

(22) Filed: **Feb. 27, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/039,218, filed on Feb. 28, 1997, and provisional application No. 60/039,407, filed on Feb. 28, 1997.

(51) **Int. Cl.**[7] **G06K 9/00**; G06K 9/34; G01J 3/40

(52) **U.S. Cl.** **382/128**; 382/165; 382/173; 356/303

(58) **Field of Search** 382/128, 162, 382/173, 274, 165; 358/504; 356/303, 346

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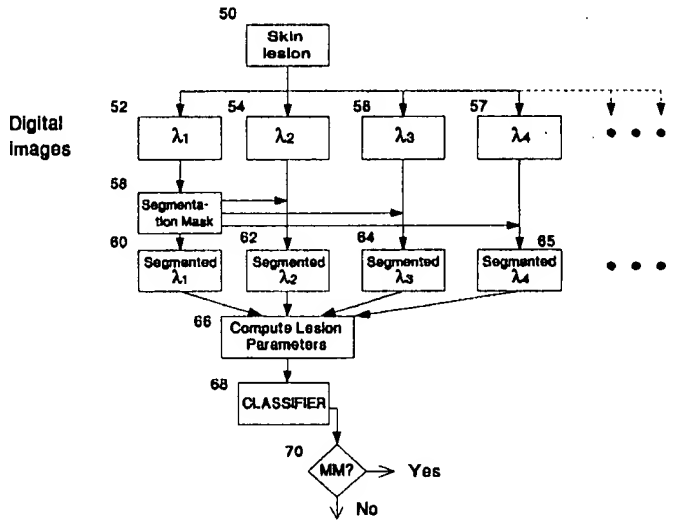
Primary Examiner—Amelia Au
Assistant Examiner—Mehrdad Dastouri
(74) *Attorney, Agent, or Firm*—Morgan & Finnegan, L.L.P.

(57) **ABSTRACT**

Systems and methods for the multispectral imaging of skin tissue enables automatic characterization of the condition of a region of interest of the skin, based on direct digital imaging of the region of interest or the digitization of color photographic slides of the region of interest, illuminated by appropriately filtered light. Preferably, a digital image at a low spectral band is automatically segmented and that segmented mask is used to segment the other images by a digital processor. Parameters related to the texture, asymmetry, blotchiness and border irregularities are also automatically estimated. The region of interest is automatically characterized by the digital processor, based on those parameters. The region of interest may include a skin lesion, in which case the present invention enables the characterization of the lesion as malignant or benign.

73 Claims, 16 Drawing Sheets



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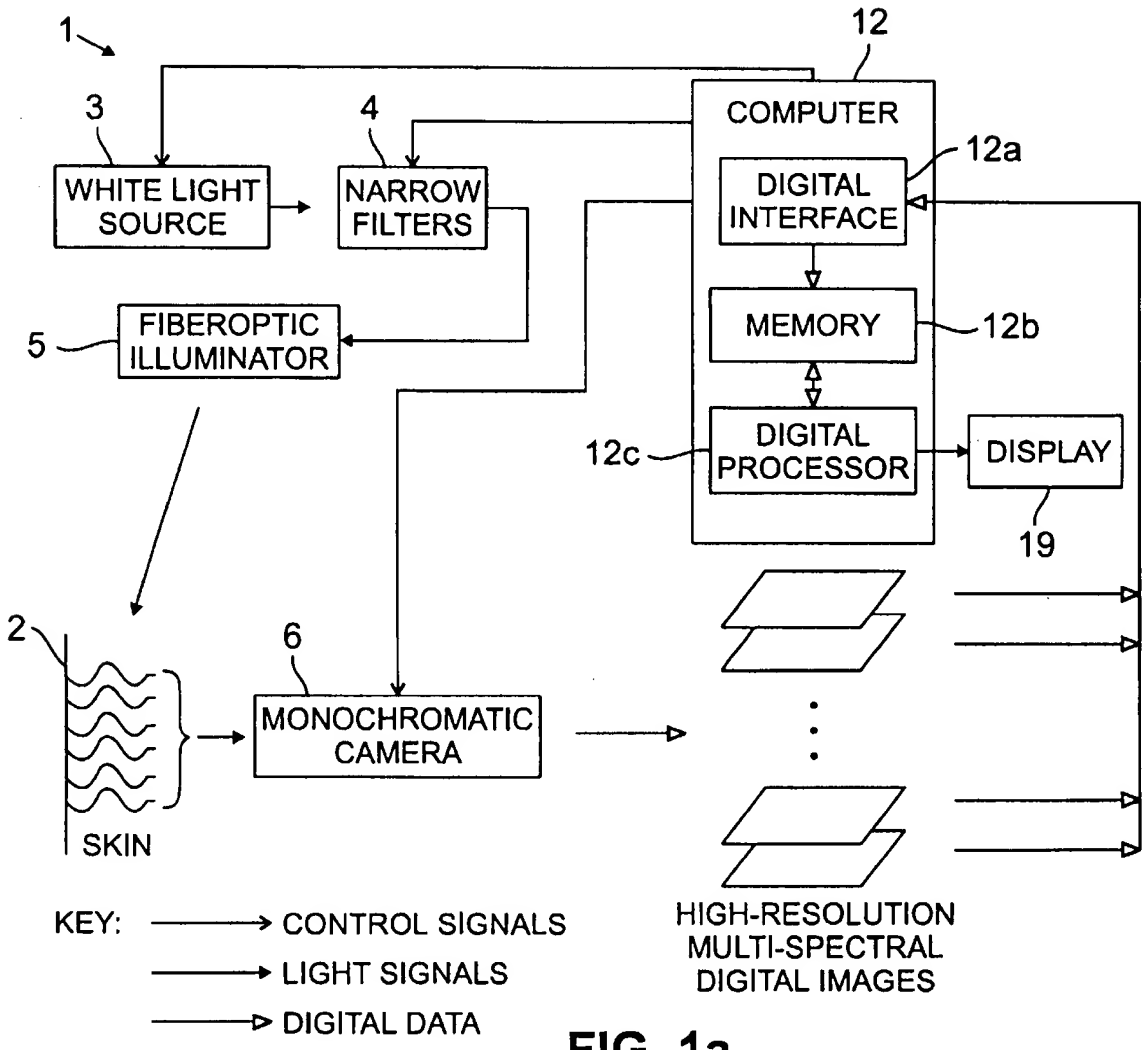

1
12
3
4
COMPUTER
12a
WHITE LIGHT SOURCE
NARROW FILTERS
DIGITAL INTERFACE
MEMORY
12b
5
FIBEROPTIC ILLUMINATOR
12c
DIGITAL PROCESSOR
DISPLAY
19
2
6
MONOCHROMATIC CAMERA
SKIN
KEY:
CONTROL SIGNALS
LIGHT SIGNALS
DIGITAL DATA
HIGH-RESOLUTION MULTI-SPECTRAL DIGITAL IMAGES

FIG. 1a

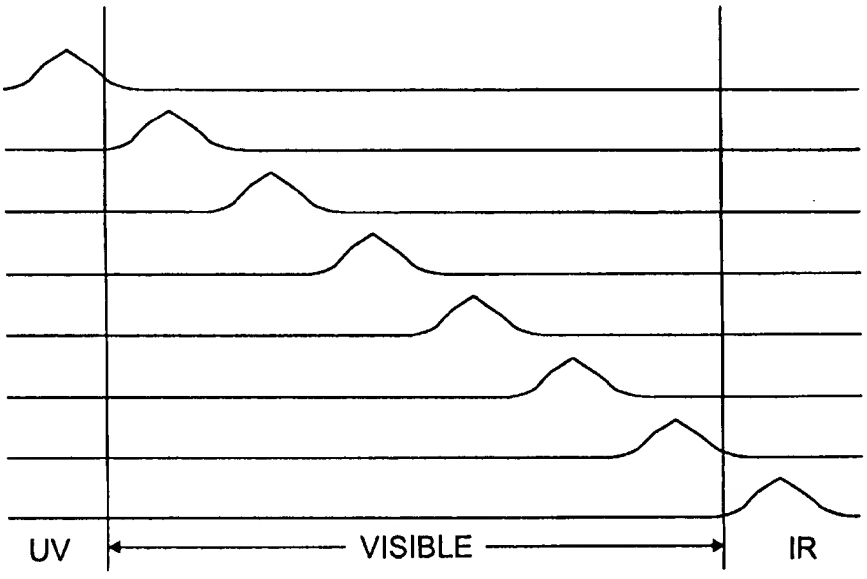
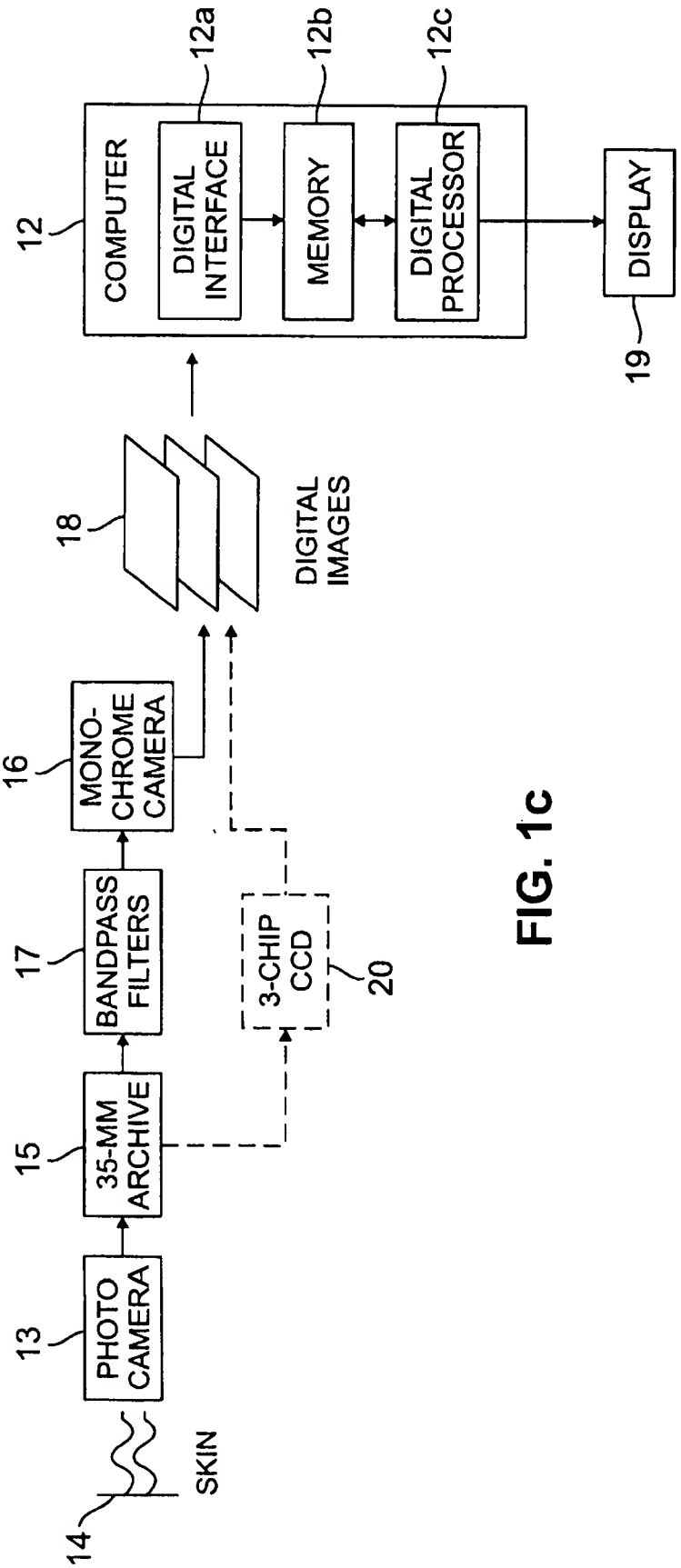

UV
VISIBLE
IR

FIG. 1b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COMPUTER
12a
DIGITAL INTERFACE
12b
MEMORY
12c
DIGITAL PROCESSOR
DISPLAY
19
18
DIGITAL IMAGES
16
MONO-CHROME CAMERA
17
BANDPASS FILTERS
3-CHIP CCD
20
15
35-MM ARCHIVE
13
PHOTO CAMERA
SKIN
14

FIG. 1c

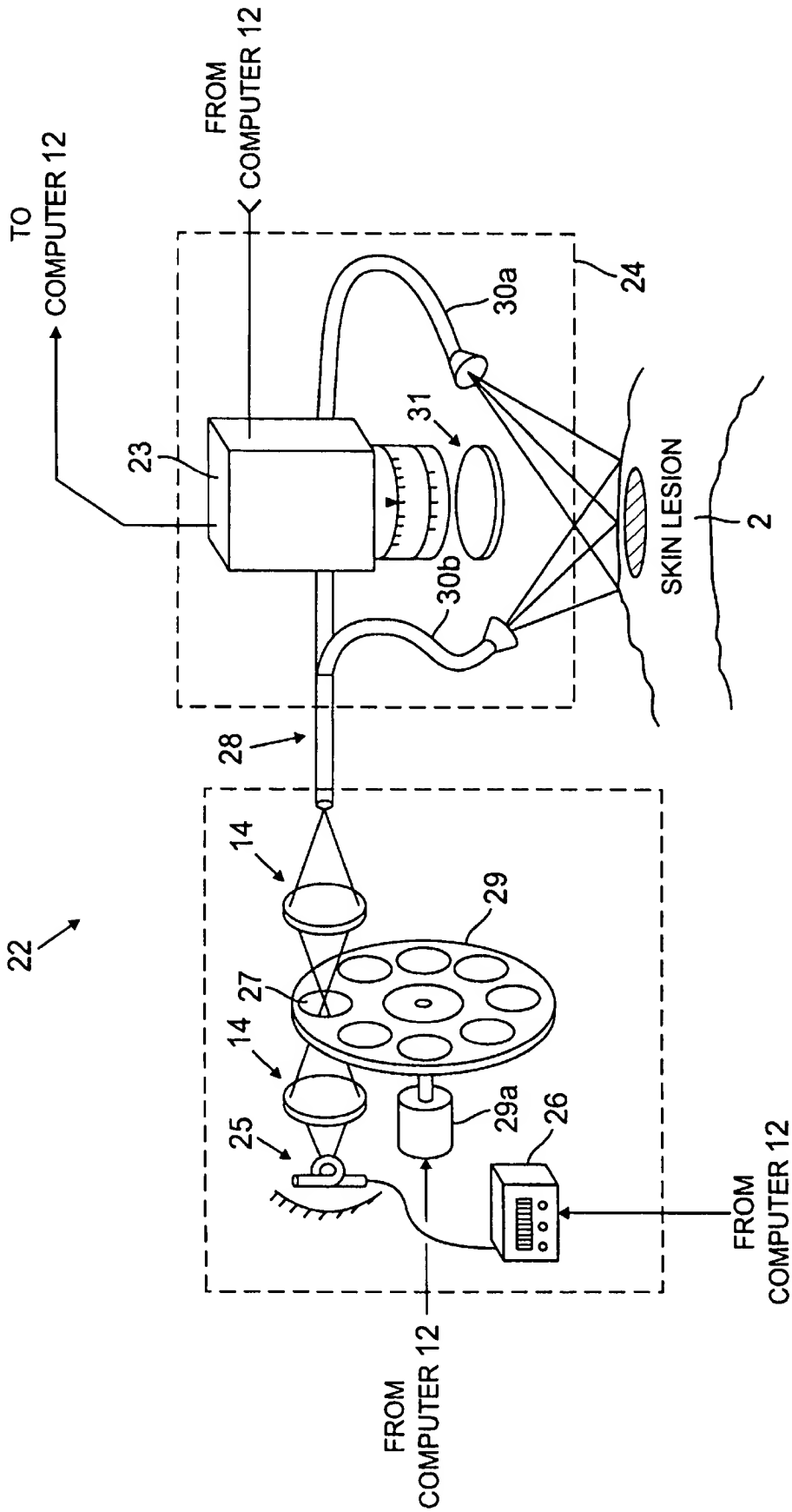

TO COMPUTER 12
FROM COMPUTER 12
24
30a
31
23
30b
SKIN LESION
2
28
22
14
29
27
14
29a
26
25
FROM COMPUTER 12
FROM COMPUTER 12

FIG. 2

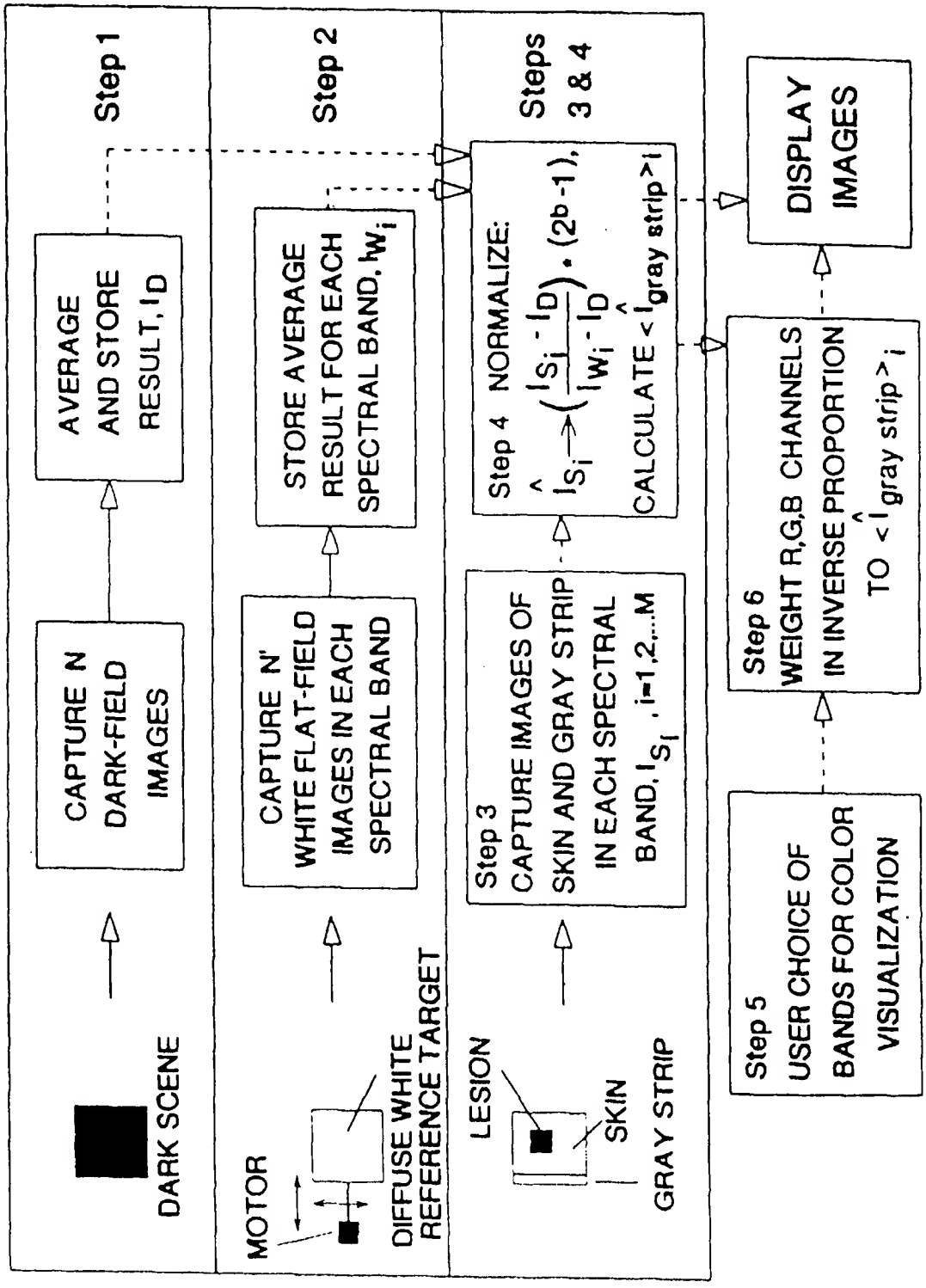

Step 1
Step 2
Steps 3 & 4
AVERAGE AND STORE RESULT, I_D
CAPTURE N DARK-FIELD IMAGES
STORE AVERAGE RESULT FOR EACH SPECTRAL BAND, W_i
CAPTURE N' WHITE FLAT-FIELD IMAGES IN EACH SPECTRAL BAND
Step 3 CAPTURE IMAGES OF SKIN AND GRAY STRIP IN EACH SPECTRAL BAND, I_{S_i}, i=1,2,...M
Step 4 NORMALIZE: $\hat{I}_{S_i} \rightarrow \left(\frac{I_{S_i} - I_D}{I_{W_i} - I_D}\right) \cdot (2^b - 1)$, CALCULATE $< \hat{I}_{gray\ strip} >_i$
DISPLAY IMAGES
Step 6 WEIGHT R,G,B CHANNELS IN INVERSE PROPORTION TO $< \hat{I}_{gray\ strip} >_i$
Step 5 USER CHOICE OF BANDS FOR COLOR VISUALIZATION
DARK SCENE
MOTOR
DIFFUSE WHITE REFERENCE TARGET
LESION
SKIN
GRAY STRIP

FIG. 3a

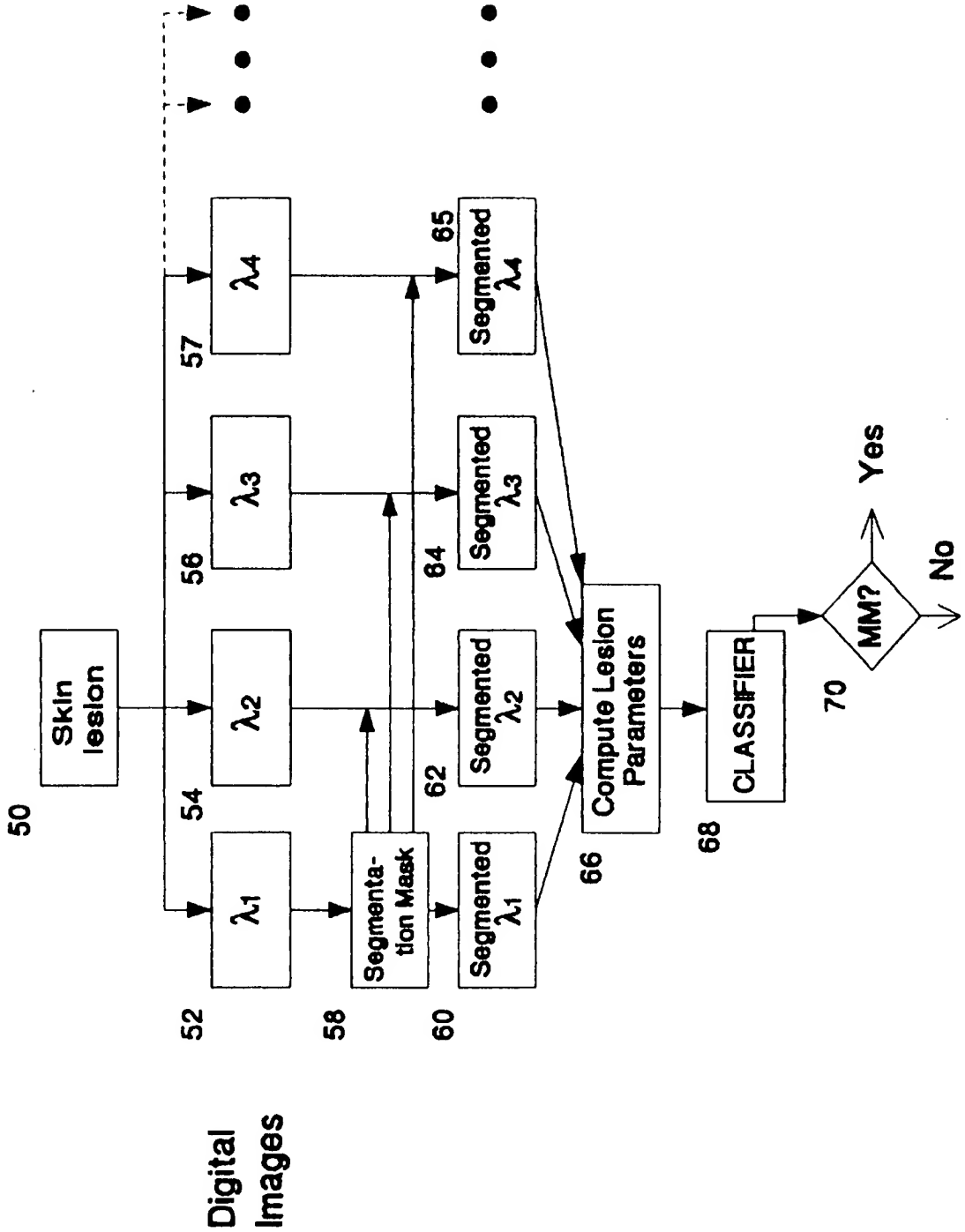
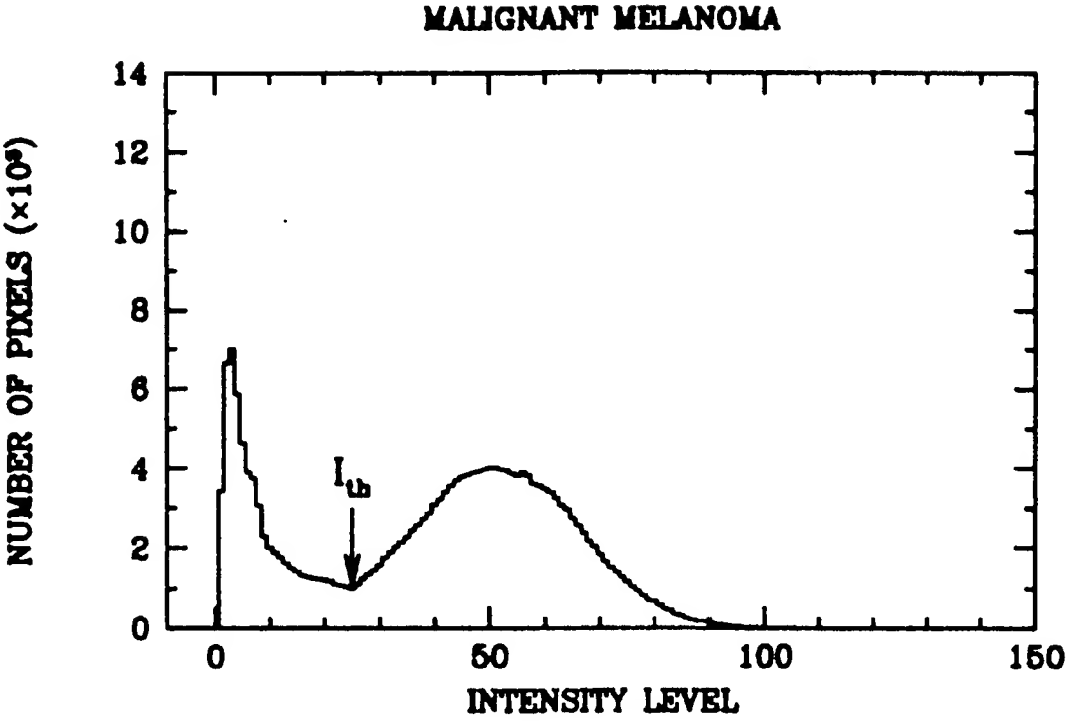

Digital Images
Skin lesion
λ1
λ2
λ3
λ4
Segmenta-tion Mask
Segmented λ1
Segmented λ2
Segmented λ3
Segmented λ4
Compute Lesion Parameters
CLASSIFIER
MM?
Yes
No
50
52
54
56
57
58
60
62
64
65
66
68
70

Fig. 3b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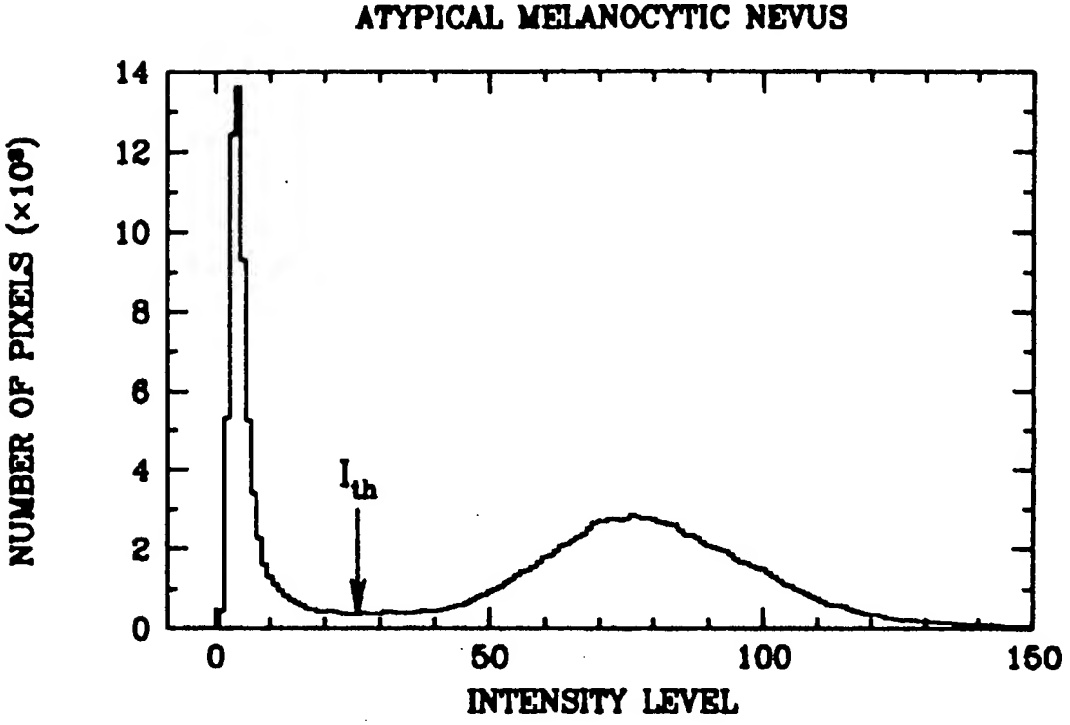
100
150
INTENSITY LEVEL

Fig. 4(a)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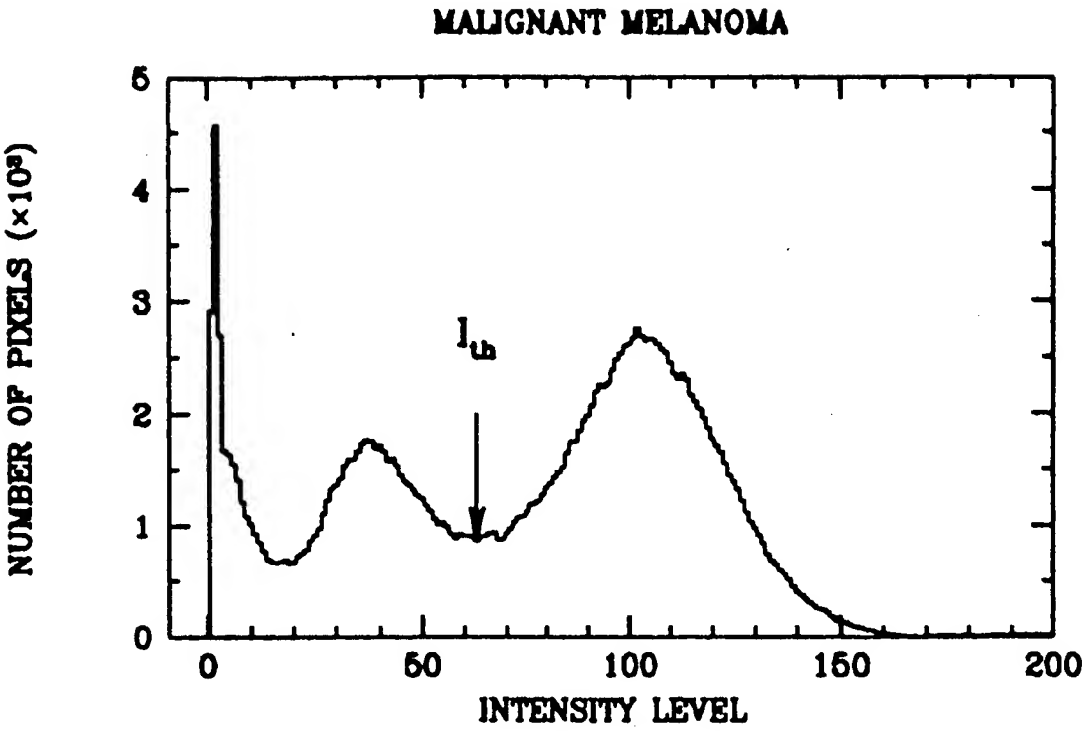
INTENSITY LEVEL

Fig. 4(b)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I_{th}
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50
100
150
200
INTENSITY LEVEL

Fig. 5(a)

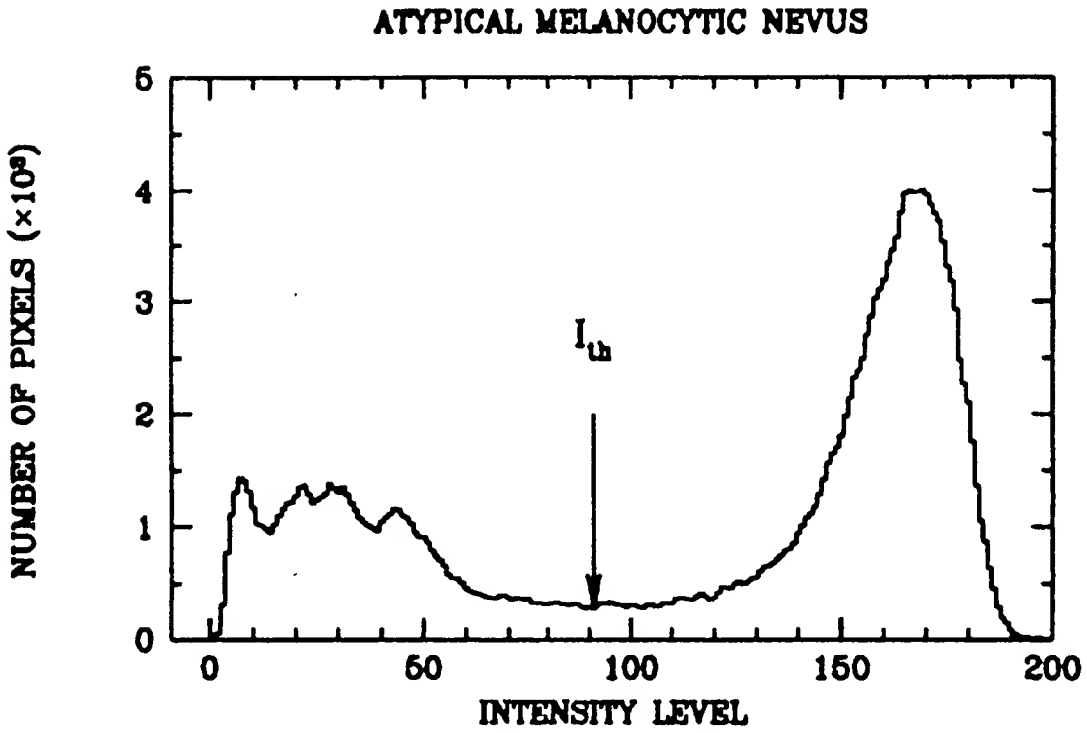
ATYPICAL MELANOCYTIC NEVUS
NUMBER OF PIXELS (×10³)
5
4
3
2
1
0
I_{th}
0
50
100
150
200
INTENSITY LEVEL

Fig. 5(b)

MALIGNANT MELANOMA

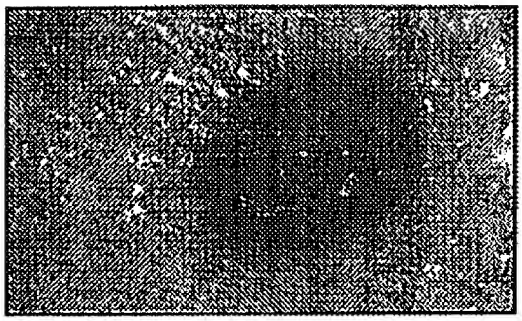

Fig. 6(a)

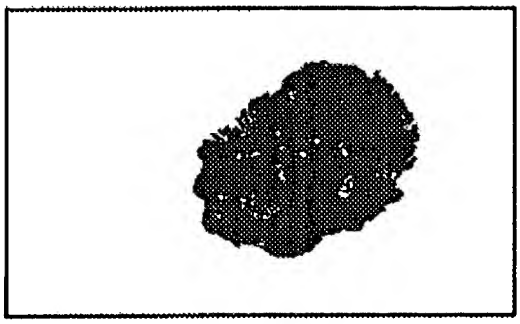

Fig. 6(b)

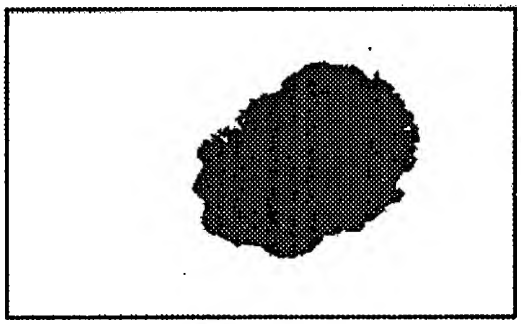

Fig. 6(c)

ATYPICAL MELANOCYTIC NEVUS

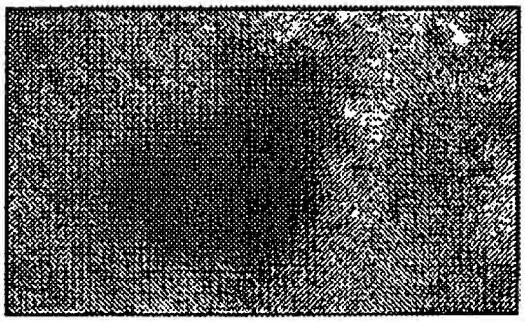

Fig. 6(d)

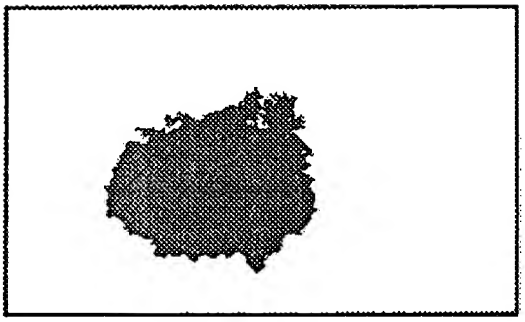

Fig. 6(e)

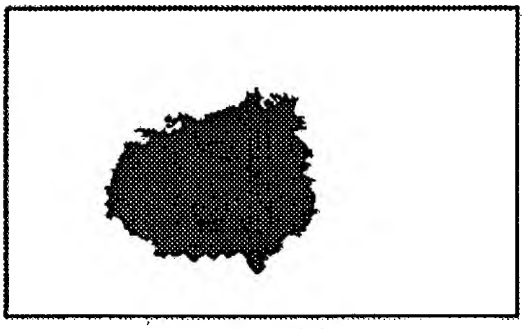

Fig. 6(f)

MALIGNANT MELANOMA

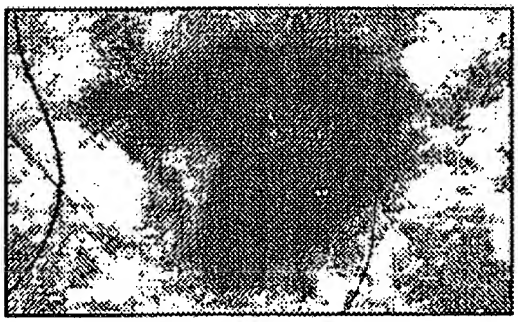

Fig. 7(a)

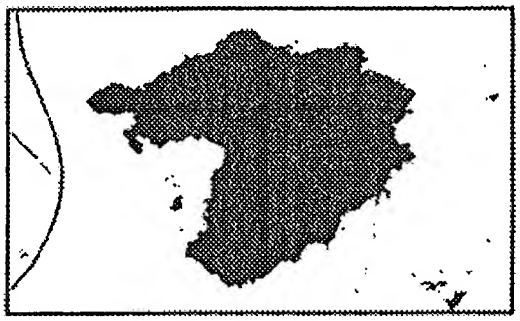

Fig. 7(b)

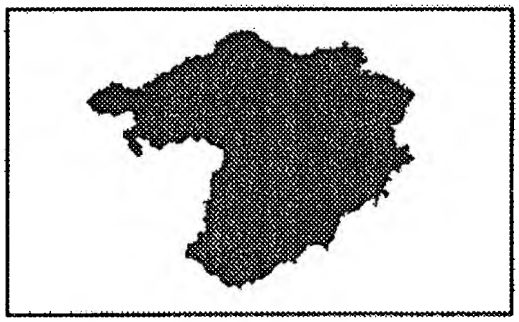

Fig. 7(c)

ATYPICAL MELANOCYTIC NEVUS

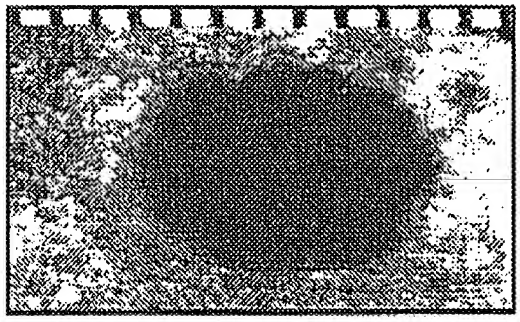

Fig. 7(d)

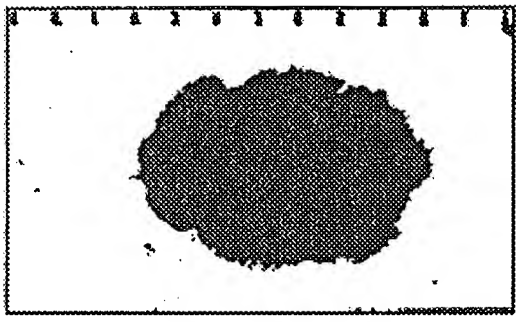

Fig. 7(e)

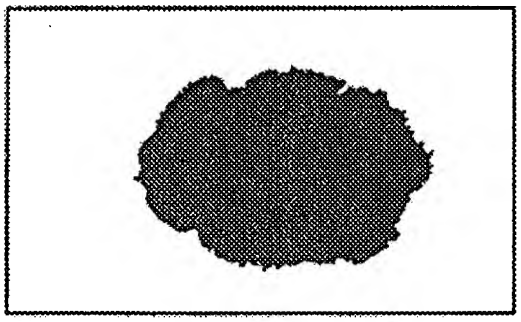

Fig. 7(f)

MALIGNANT MELANOMA

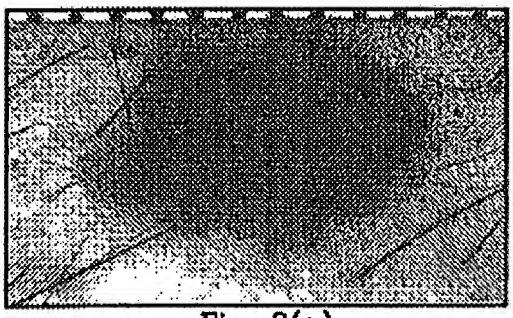

Fig. 8(a)

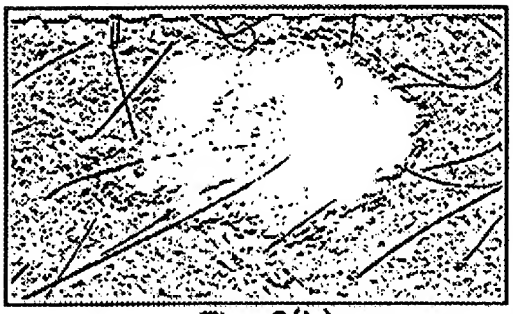

Fig. 8(b)

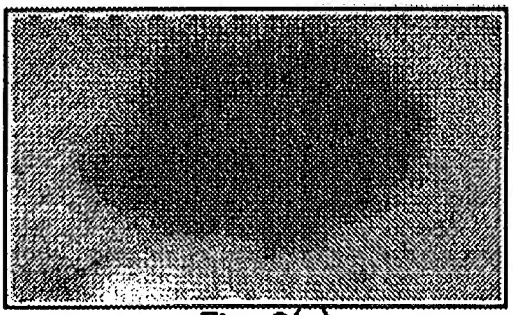

Fig. 8(c)

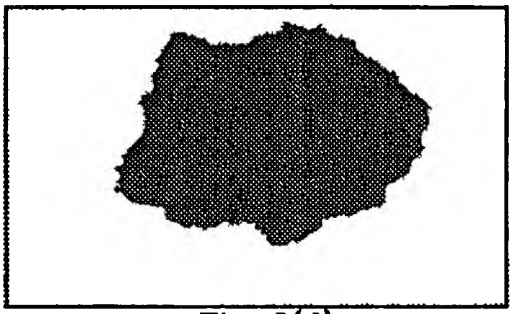

Fig. 8(d)

ATYPICAL MELANOCYTIC NEVUS

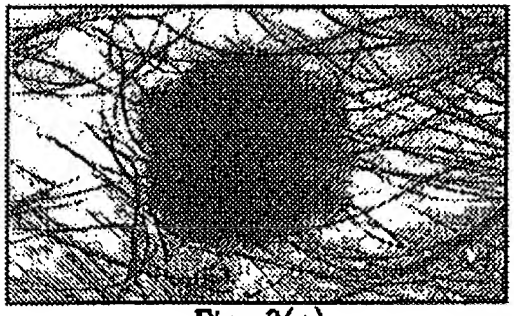

Fig. 8(e)

Fig. 8(f)

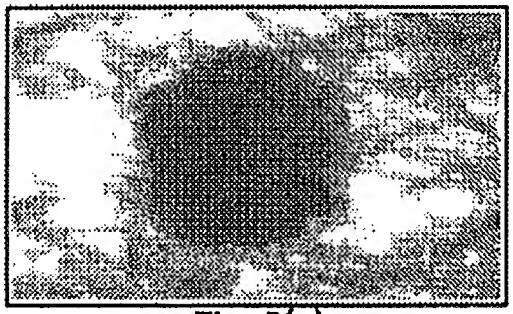

Fig. 8(g)

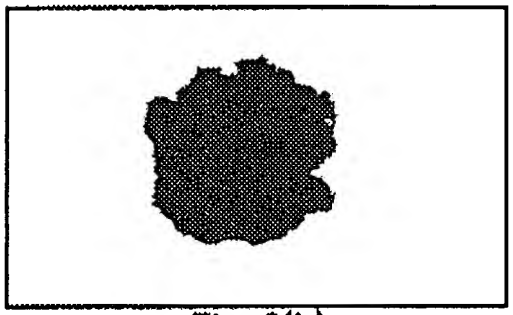

Fig. 8(h)

	I-3	I-2	I-1	I	I+1	I+2	I+3
J-5	0	1	0	0	0	1	0
J-4	0	1	1	0	1	1	0
J-3	0	0	2	3	2	0	0
J-2	1	0	0	1	0	0	1
J-1	1	0	-3	-5	-3	0	1
J	1	1	-5	-8	-5	1	1
J+1	1	0	-3	-5	-3	0	1
J+2	1	0	0	1	0	0	1
J+3	0	0	2	3	2	0	0
J+4	0	1	1	0	1	1	0
J+5	0	1	0	0	0	1	0

Fig. 9

MALIGNANT MELANOMA

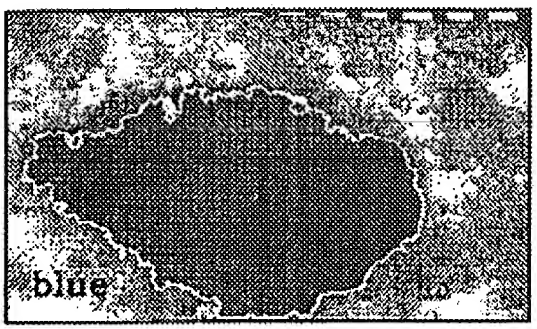

Fig. 10(a)

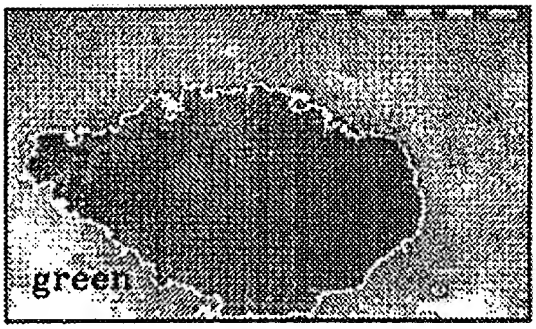

Fig. 10(b)

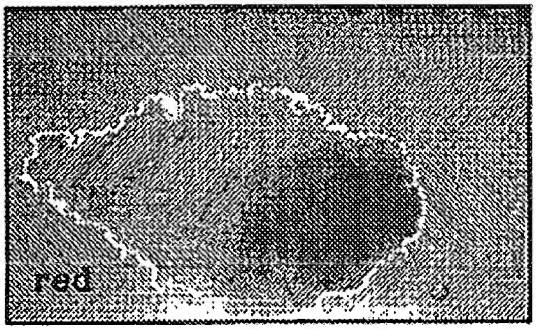

Fig. 10(c)

ATYPICAL MELANOCYTIC NEVUS

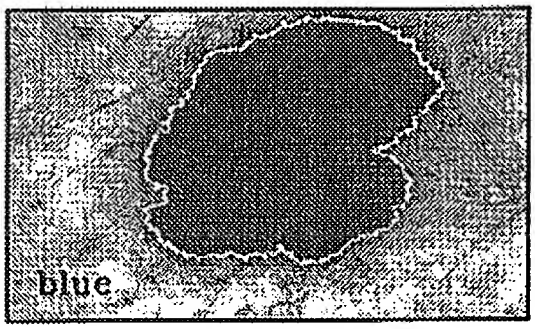

Fig. 10(d)

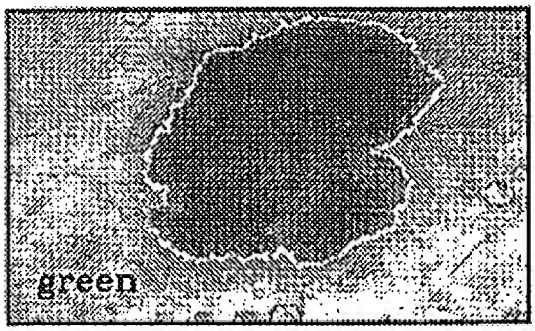

Fig. 10(e)

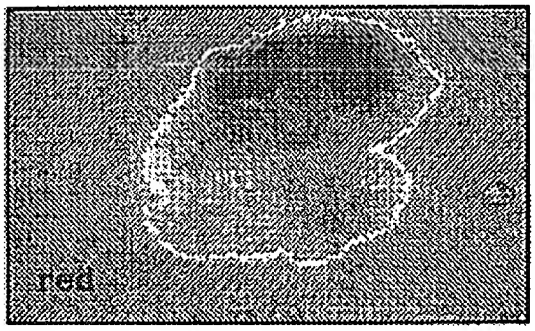

Fig. 10(f)

PARAMETER		Diagnostic accuracy (%)	Sensitivity (%)	Specificity (%)
Asymmetry:	A_{bin}	52	71	86
	A_b	48	68	84
	A_g	50	73	82
	A_r	62	78	89
Blotchiness:	Bl_b	45	56	90
	Bl_g	40	68	72
	Bl_r	42	68	75
	C_b	37	80	55
	C_r	38	80	57
	Cl	44	78	70
Border:	B	44	66	81
	G_b	36	76	56
Texture:	$T1_b$	38	88	49
	$T1_g$	49	61	90
	$T2_g$	41	66	76
	$T2_r$	43	73	72
	$T3_b$	39	80	59
	$T3_g$	38	63	74
	$T4_b$	38	68	69
	$T4_g$	39	56	83
	$T5_b$	36	76	58
	$T6_b$	38	90	46

Fig. 11

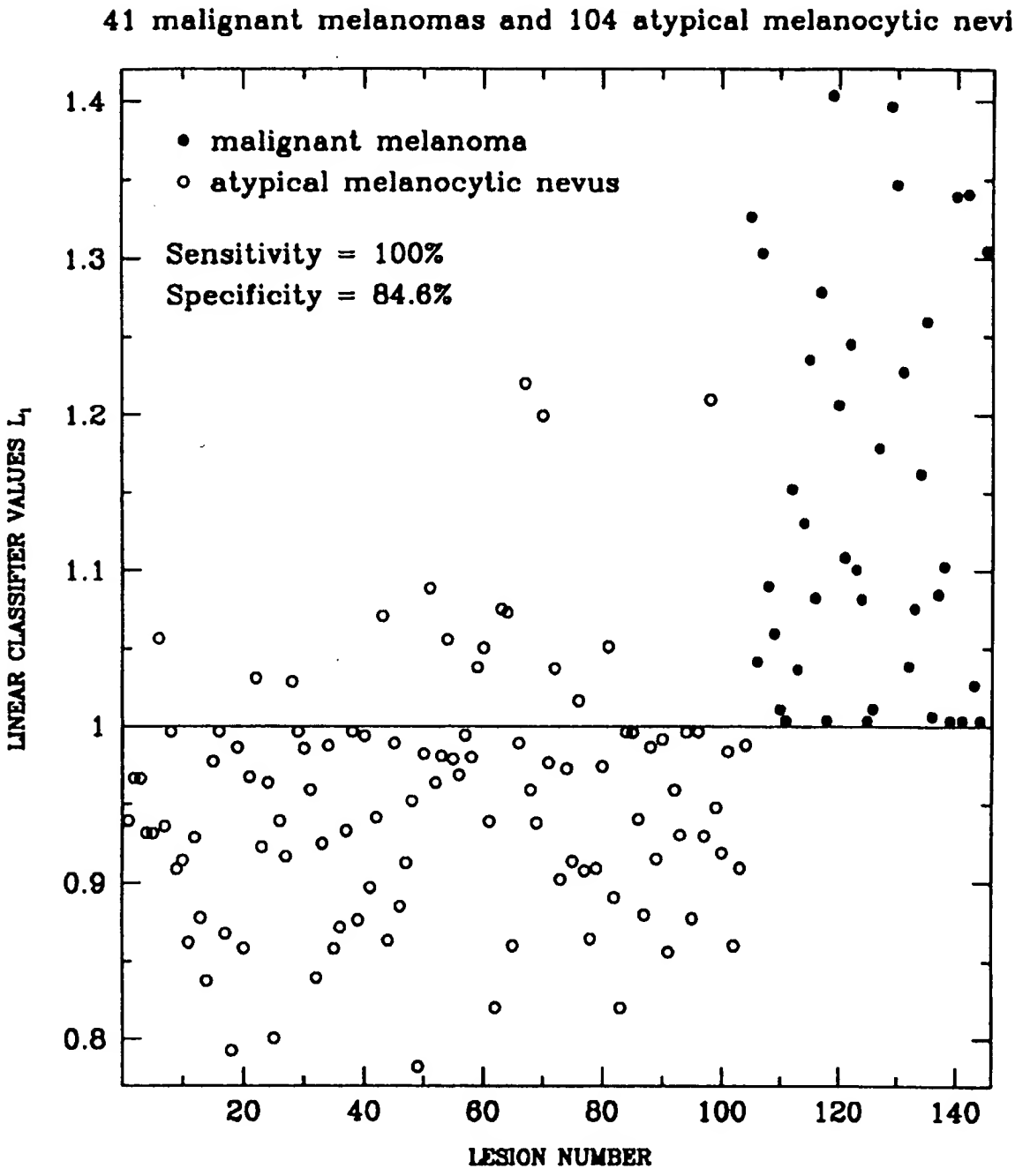
41 malignant melanomas and 104 atypical melanocytic nevi
• malignant melanoma
o atypical melanocytic nevus
Sensitivity = 100%
Specificity = 84.6%
LINEAR CLASSIFIER VALUES L_1
1.4
1.3
1.2
1.1
1
0.9
0.8
20
40
60
80
100
120
140
LESION NUMBER

Fig. 12

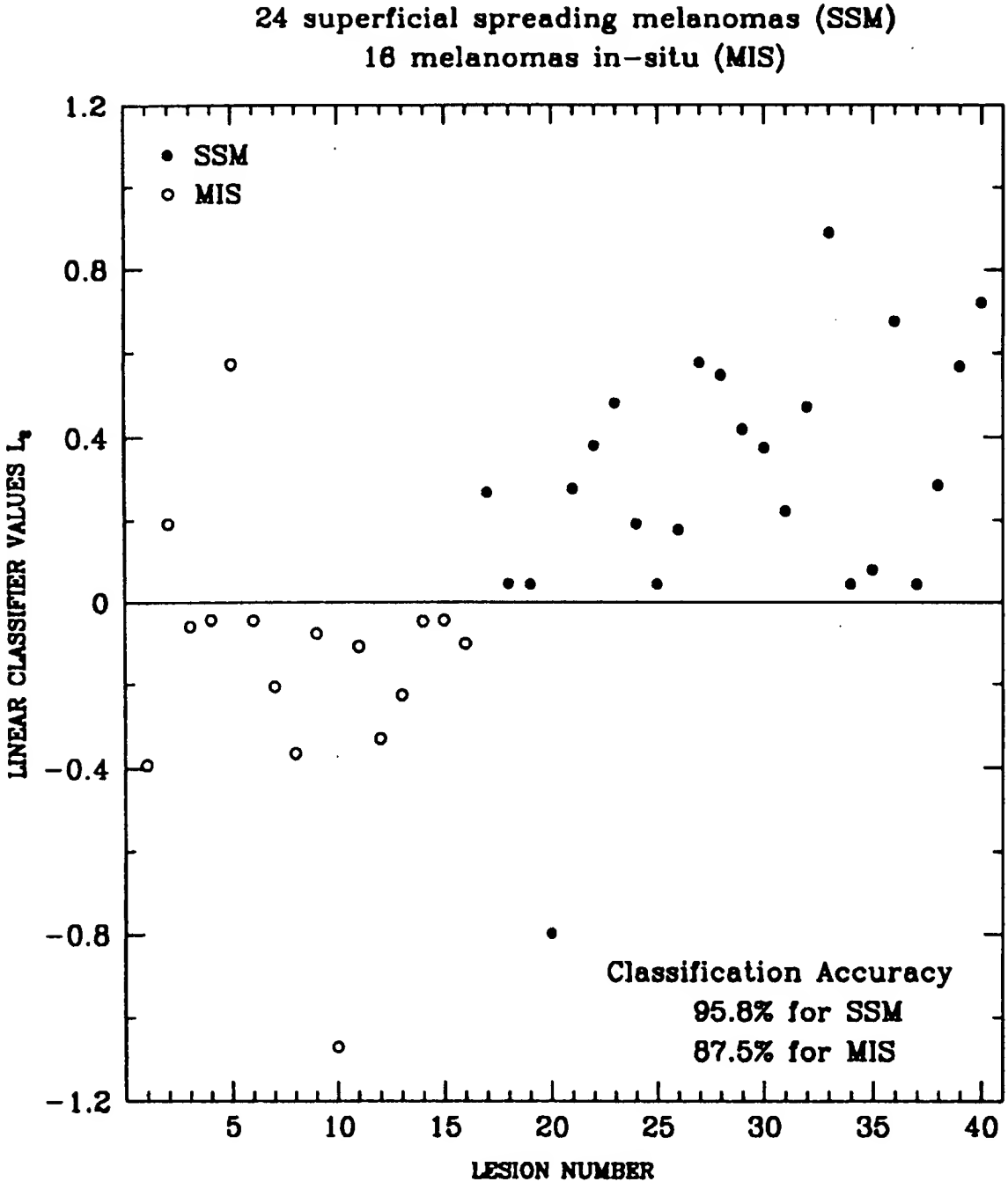
24 superficial spreading melanomas (SSM)
16 melanomas in-situ (MIS)
SSM
MIS
1.2
0.8
0.4
0
-0.4
-0.8
-1.2
LINEAR CLASSIFIER VALUES L_F
5
10
15
20
25
30
35
40
LESION NUMBER
Classification Accuracy
95.8% for SSM
87.5% for MIS

Fig. 13

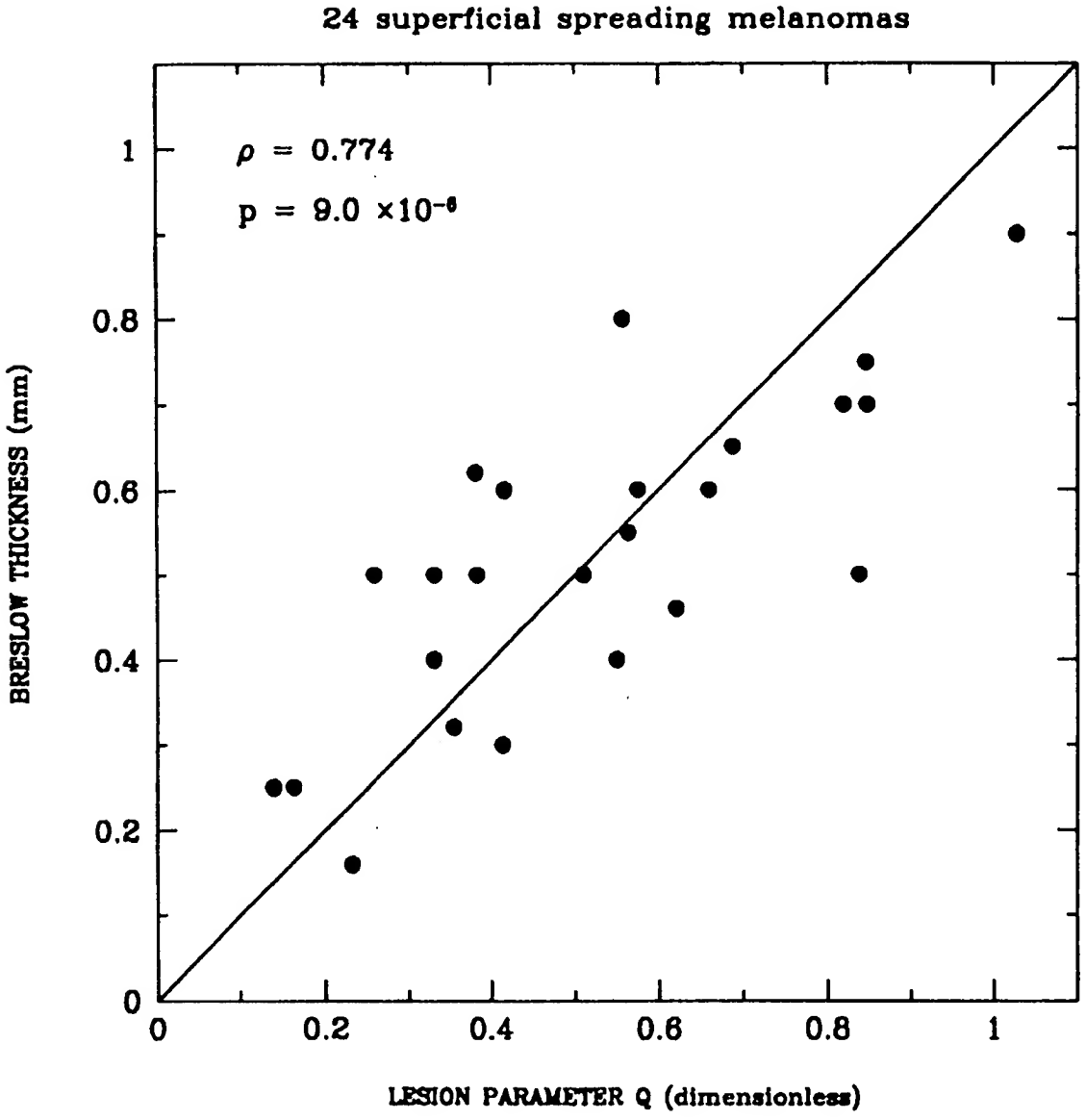
24 superficial spreading melanomas
ρ = 0.774
p = 9.0 ×10⁻⁶
BRESLOW THICKNESS (mm)
LESION PARAMETER Q (dimensionless)
0
0.2
0.4
0.6
0.8
1

Fig. 14

SYSTEMS AND METHODS FOR THE MULTISPECTRAL IMAGING AND CHARACTERIZATION OF SKIN TISSUE

This application claims the benefit of U.S. provisional application Ser. Nos. 60/039,218 and 60/039,407, both of which were filed on Feb. 28, 1997, and are incorporated by reference, herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with Government support under NIH/National Cancer Institute Contract No. 2-R44-CA60229-02A1 and U.S.A.F. Phillips Laboratory Contract No. F29601-95-C-0125. The Government has certain rights in this invention.

FIELD OF THE INVENTION

This invention relates to methods and systems for the computer controlled image analysis of digital skin tissue at a plurality of wavelengths, which may include those outside of the red-green-blue bands. The methods and systems further include the automatic characterization of the condition of the skin tissue, based on automatically computed values of parameters which are functions of characteristics of the skin tissue, based on the digital images. Skin lesions can be analyzed for determining whether the lesion is a melanoma, for example. Systems for digitally imaging and analyzing skin tissue are disclosed, as well.

BACKGROUND OF THE INVENTION

Melanoma is a usually fatal skin cancer, unless it is detected and surgically removed in its earliest stages. Early detection of malignant melanoma is difficult because early melanomas, those having a Breslow thickness less than 1 mm, share many diagnostic features with benign lesions, such as dysplastic nevi or atypical melanocytic nevi.

To aid in the analysis of lesions, conventional photography, referred to as "clinical imaging", has been used to image the lesion for further study. The effectiveness of clinical imaging can be compromised, however, by specular reflection by the skin. Polarizers have been used for polarized imaging, which minimizes specular reflection.

Dermoscopy is another technique for examining skin, in which specular reflection is minimized. Dermoscopy also assists in clinically differentiating melanoma from its benign simulants by enabling the observation of features of pigmented melanocytic lesions that are not discernible by the naked eye. In dermoscopy, the skin is made more transparent to light by providing an oil layer over the skin, in front of the optical system. A glass plate is placed over the oil layer. The oil has an index of refraction between the index of refraction of the horny layer of the skin and the glass plate. Standard magnifying optics may be used to enlarge the structures rendered visible on and under the surface of the skin by the oil layer. The region of interest can then be examined visually. Slides of the region of interest can be made, as well, for future study.

Despite their similarities, most malignant melanomas differ in certain of their characteristics from other melanocytic lesions. A major advance in characterizing skin lesions based on certain of the observable differences between malignant and other lesions is the "ABCD" rule, where A=asymmetry, B=border irregularity, C=color variability, and D=diameter greater than 6 mm. A corresponding ABCD rule, where "D" refers to dermoscopic structures, such as brown globules, black dots or pigment networks within the lesion, is applied to dermoscopic images. Because the clinical and dermoscopic applications of these rules are subjective, they are not very reliable.

When skin is illuminated by light, the light can be re-emitted by reflection, scattering or fluorescence. It is known in the art that the re-emission of light absorbed at different wavelengths by a region of interest of skin can provide different information. For example, as the wavelength of the light increases, its depth of penetration into the skin or other tissue also increases. Chromophores at different depths in the tissue therefore absorb and re-emit light at various wavelengths. Melanin and hemoglobin are examples of such chromophores.

Since the unaided eye cannot perceive light outside of the visible region or low-contrast structure in visible-light images, information which may be useful in diagnosing a lesion may not be directly observable. Digital acquisition and processing of dermoscopic images may, therefore, improve diagnostic reliability by employing more of the information residing in such images that is not directly observable. There have therefore been attempts to use objective, computer-based, image analysis algorithms that can discern meaningful differences between benign and malignant melanocytic lesions with sufficient accuracy.

Computer processing of images requires that the image be in digital form. A digital image is an array of digital signals whose values are a function of certain characteristics of the subject of the image. When imaging skin lesions, the digital images comprise digital signals whose values are a function of the re-emission characteristics of the skin and lesion, at different spectral bands of light. The array is obtained by spatial sampling and quantizing the intensity of images obtained with film or directly by electronic cameras. Practical limitations on the number of picture elements or pixels per unit area of image determine the achievable spatial resolution of the digital image. The digital image typically needs to be segmented to separate the digital signals which are a function of the skin lesion from the digital signals which are a function of the surrounding skin.

Computer aided analysis has also been used to classify skin lesions using quantitative values indicative of particular characteristics of lesions, referred to as parameters. Based on histopathological diagnosis of lesions, algorithms have been developed which use linear or non-linear classifiers to combine parameters provided by the operator of an imaging device or a physician or computed by a processor, to yield a value which can be used to classify the lesion. Because some of the steps in the computer-aided analysis of which we are aware depend on subjective judgments of an individual, such analyses may provide highly variable results.

The images heretofore available have been obtained with commercially available red-green-blue color imaging apparatus. Color photographic transparencies of skin lesions have been digitized and skin lesions have been directly imaged with "three-chip" digitizing cameras. Such cameras employ broad-band filter bandpasses that are ultimately based on the wavelength response of the human visual system and have large regions of overlap.

Electronic images may also be obtained in narrower, non-overlapping filter bandpasses, which may reveal additional, wavelength-dependent differences between the images of melanomas and of benign lesions. However, such devices have had poor resolution and/or poor signal-to-noise

characteristics which prevent the acquisition of digital images of melanocytic skin lesions of sufficient quality for effective application of machine vision techniques for lesion diagnosis.

Existing imaging systems and processes also tend to suffer from an inability to provide the required repeatability of the values of extracted lesion parameters, due in part to a lack of standardization with respect to spatially varying artifacts. The parameters, therefore, lack invariance to lighting and image exposure conditions, for example. Obtaining high signal-to-noise ratios in images recorded in narrow filter bandpasses, when exposure times are sufficiently short that the skin is effectively "frozen" during the exposure sequence, has also been difficult. In addition, since the optimum wavelengths for automatic characterization may not be the optimum wavelengths for visual observation, it may be difficult to reconstruct high-fidelity color images from the digital images for visual interpretation by a clinician.

The assessment of wounds and burns through the appearance of color images present similar challenges. Existing technology for the imaging of skin in vivo for these purposes is also inadequate. Practical solutions to the problems of employing multispectral digital imaging of skin for the analysis of lesions, wounds, or other conditions have not been found.

SUMMARY OF THE INVENTION

The methods and systems of the present invention provide for the acquisition of digital images of skin at a plurality of spectral bands to automatically characterize the condition of the tissue based on the digital images. Spectral wavelength bands within and outside of the visible band may be used. In accordance with the present invention, a pigmented skin lesion can be characterized as malignant or benign, for example. The digital images comprise a plurality of digital signals whose values are functions of the condition of the tissue. The digital images acquired are subjected to objective and quantitative analysis by a digital processor to detect and identify abnormalities. The analysis includes image segmentation, parameter estimation and characterization of the skin. The estimation and characterization steps are automatic. The segmentation step may be automatic, as well. Subjective judgments are therefore minimized or eliminated.

It has been found that generating the segmentation mask from a digital image acquired with light in a spectral band which does not penetrate deeply into the skin, such as a blue spectral band, provides superior results. After segmentation, estimated values which are functions of characteristics of the lesion, such as its texture, asymmetry, blotchiness, and border irregularities, are computed and used to automatically characterize the condition of the skin. Digital signals corresponding to hair or blob-like structures are preferably removed during segmentation.

In accordance with the present invention, a method for characterizing the condition of a region of interest of the skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, is disclosed. The method comprises illuminating the region of interest of the skin by light in at least three spectral bands and digitally imaging the region of interest at the at least three spectral bands with the light re-emitted by the skin to generate digital images comprising digital signals whose values are a function of the condition of the skin. The digital images are provided to a processor which segments the digital images by generating a segmentation mask from a digital image in any one of the at least three spectral bands, computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the region of interest within the segmentation mask, characterizes the condition of the skin based on the estimated values, and outputs the characterization of the condition of the skin. Preferably, the segmenting, estimating and characterizing steps are conducted without the intervention of an operator. Useful parameters include measures of the texture, asymmetry, blotchiness and border irregularity of the portion of the region of interest.

The digital images may be obtained by directly imaging the region of interest with a digital camera, or digitally imaging color slides of the region of interest, through appropriately filtered light.

The characterizing step may include comparing a weighted combination of the parameter values against a threshold value. The weight coefficients for each parameter value and the threshold value may be selected based on a training set of images of lesions or other skin conditions, whose condition has been determined, preferably through histological examination by a plurality of doctors. Preferably, specificity is maximized under the constraint of 100% sensitivity to melanoma.

In accordance with another aspect of the invention, a system for characterizing the condition of a region of interest of skin includes means for illuminating the region of interest with light in at least three spectral bands and a camera for acquiring digital images of the region of interest based on the light re-emitted from the illuminated region of interest at each of the spectral bands. The digital image comprises digital signals whose values are a function of the condition of the region of interest. A digital processor segments the digital images by generating a segmentation mask from a digital image in any one of the at least three spectral bands, and computes at least one estimated value for each digital image at each spectral band which is a function of the texture of the portion of the region of interest within the segmentation mask. The processor characterizes the lesion based on the estimated value or values. The other parameters discussed above may be used, as well.

The camera may be a single-chip or multiple-chip charge-coupled device which detects light in a plurality of spectral bands between the near ultraviolet to near infrared. The filter means may be a plurality of interference filters mounted on a wheel for stepping any filter into a position intercepting the light from the light source. Preferably, at least one of the spectral bands has a center which lies between about 400 and 500 nanometers, at least one of the spectral bands has a center which lies between about 500 and 600 nanometers, and at least one other spectral band has a center which lies between about 750 and 1000 nanometers.

DESCRIPTION OF THE FIGURES

FIG. 1(*a*) is a schematic illustration of a method and system of imaging a region of interest of skin in accordance with the present invention;

FIG. 1(*b*) is a schematic illustration of a plurality of narrow spectral bandwidths which may be used to illuminate the skin in the embodiment of FIG. 1(*a*);

FIG. 1(*c*) is a schematic illustration of alternative methods and systems for digitizing and analyzing color photographic slides of a region of interest of skin;

FIG. 2 is a schematic illustration of preferred illumination and imaging portions of a computer controlled imaging system for direct imaging of a lesion;

FIG. 3(*a*) is a flow chart of a calibration procedure for use with the present invention;

FIG. 3(*b*) is a flow chart of a method of processing images for classifying lesions as malignant or benign, in accordance with the present invention;

FIGS. 4(*a*) and 4(*b*) are histograms of a malignant melanoma and of an atypical melanocytic nevus, respectively, showing two peaks in each histogram;

FIGS. 5(*a*) and 5(*b*) are histograms of another malignant melanoma and another atypical melanocytic nevus, respectively, showing three or more peaks in each histogram;

FIGS. 6(*a*) and 6(*d*) are digital images in the blue spectral band of another malignant melanoma and another atypical melanocytic nevus, respectively;

FIGS. 6(*b*) and 6(*e*) are digital images of the images of FIGS. 6(*a*) and 6(*d*) respectively, after thresholding;

FIGS. 6(*c*) and 6(*f*) are digital images of the images of FIGS. 6(*a*) and 6(*d*), respectively, after iterative thresholding;

FIGS. 7(*a*) and 7(*d*) are digital images in the blue spectral band of another malignant melanoma and another atypical melanocytic nevus;

FIGS. 7(*b*) and 7(*e*) are digital images of FIGS. 7(*a*) and 7(*d*), respectively, resulting from iterative processing and showing dark blobs outside the lesion area;

FIGS. 7(*c*) and 7(*f*) are digital image masks of FIGS. 7(*b*) and 7(*d*), respectively, resulting from image cleaning;

FIGS. 8(*a*) and 8(*e*) are digital images in the blue spectral band of another malignant melanoma and another atypical melanocytic nevus, respectively, showing hair;

FIGS. 8(*b*) and 8(*f*) are reverse intensity contrast images of the lesions of FIGS. 8(*a*) and 8(*e*), respectively;

FIGS. 8(*c*) and 8(*g*) are digital images resulting from an averaging process applied to the images of FIGS. 8(*a*) and 8(*b*), to remove hair;

FIGS. 8(*d*) and 8(*h*) are binary lesion masks resulting from the segmentation of the images of FIGS. 8(*c*) and 8(*g*), respectively;

FIG. 9 is a spatial filter used to remove hair;

FIGS. 10(*a*)–10(*c*) are segmented digital images in the blue, green and red spectral bands, of the malignant melanoma whose histogram is shown in FIG. 5(*a*);

FIGS. 10(*d*)–10(*f*) are segmented digital images in the blue, green and red spectral bands, of an atypical melanocytic nevus whose histogram is shown in FIG. 5(*b*);

FIG. 11 is a chart of lesion parameters and their associated diagnostic accuracy, sensitivity and specificity when used individually;

FIG. 12 is a plot of linear classifier values versus lesion identification number, for 41 malignant melanomas and 104 atypical melanocytic nevi;

FIG. 13 is a plot of linear classifier values versus lesion identification number for 24 superficial spreading melanomas and 16 melanomas in-situ; and

FIG. 14 is a plot of lesion parameter versus Breslow thickness for 24 superficial spreading melanomas.

DESCRIPTION OF THE INVENTION

FIG. 1(*a*) is a schematic illustration of a method and system 1 in accordance with the present invention, by which images of the skin 2 are acquired by a camera nearly simultaneously at a plurality of spectral bands, λ_i, i=1,2, . . . M, that are preferably effectively non-overlapping, as shown schematically in FIG. 1(*b*). The skin is illuminated by a source of white light 3, which is filtered by narrow passband filters 4. The filtered light is preferably conveyed to the skin 2 through a fiberoptic illuminator 5. The light re-emitted by the illuminated skin is imaged by a low-noise, high-resolution monochrome camera 6, which is preferably an electronic charge-coupled ("CCD") camera. Digital images output by the camera 6 are provided to a computer 12 for processing.

The computer 12 includes a digital interface 12*a*, a memory 12*b* and a digital processor 12*c*. A display 19 is preferably provided as well. The computer 12 includes an input to a digital interface 12*a* for receiving the digital images. A memory 12*b* stores the digital images, and the software controlling operation of the imaging system, the image processing, and the classification and characterization of the lesion. The digital processor 12*c*, under control of the software, performs the calculations. The computer 12 has an output connected to a display 19, which can display the processed images and the results of the classification and characterization procedures for each image. The computer 12 also preferably has outputs connected to the source of light 3 and the camera 6, for controlling their illumination level and exposure times, respectively, as described below.

The image processing, classification or characterization and other programs can be implemented on a personal computer, using a programming language, such as FORTRAN or C. The memory 12*b* which stores the software can be any convenient media readable by the computer 12, such as the hard drive of the computer, read only memory, random access memory with a battery backup, electrically programmed ROM, electrically erasable ROM, floppy disc, or CD ROM. Other suitable media may be used, as well.

When the filter bandpasses have minimal overlap, as in FIG. 1(*b*), each monochromatic image will contain spectrally independent information. Such spectral separation is believed to be useful for differential diagnosis of skin lesions that contain varying amounts of melanin, and of hemoglobin in different oxidation states, for example. Spectral separation is also believed to be useful in distinguishing granulation of tissue and other structural details of wounds in various stages of healing. One or more of the wavelength bands may lie outside the visible region, such as in the near infrared and/or the near ultraviolet, as long as the wavelength is within the response range of the combined optical system including the electronic camera 6.

In accordance with another aspect of the invention, the digital images of skin lesions can be derived from color slides of the lesions obtained by clinical imaging, dermoscopy, or polarization imaging. FIG. 1(*c*) is a schematic illustration of alternative approaches to the acquisition and digitization of images of skin lesions from color slides. A photo camera 13 produces 35-mm color slides of a region of the skin 14. The camera 13 can be a Dermaphot® camera from Heine, Optotechnik Gmbh & Co. AG, Germany, for example. The slides are typically stored in an archive 15. The slides are subsequently reimaged by a monochrome camera 16, which may be a CCD camera, that photographs each slide as it is illuminated by white light that has passed through a sequence of bandpass filters 17 to create a color filtered version of the image. The slides can be illuminated at broad or narrow blue (B), green (G) and red (R) wavelength bands, respectively. The broad wavelength bands may overlap somewhat. In one example, the blue wavelength band was about 400 nm±30 nm, the green wavelength band was about 550 nm±30 nm, and the red wavelength band was about 700 nm±30 nm.

Each of the filtered representations is recorded by the monochrome camera **16**, which provides the resulting digital images **18** to an input of the computer **12**. If a CCD camera is not used, the slide images could be digitized by any available commercial digitizer including three channels, one for red, one for green and one for blue, as long as the pixel size in the lesion plane after digitization is less than about 60 micrometers ("μm").

An appropriate CCD camera **16** is available from Electrim, Inc., Princeton, N.J. The camera **16** has a photographic macro-lens, wherein f#/2.8 and f=100 mm. Preferably, the spatial resolution of the CCD camera **16** provides pixels having a size about 10–30 μm in the lesion plane. The CCD camera **16** from Electrim, Inc., has 753×488 pixels. The spatial resolution with such a camera is approximately 21×24 μm at the lesion plane. Digital images of lesions obtained with this imaging system were used to classify lesions as malignant or benign, and to characterize lesions as invasive or non-invasive, as described further, below. The Electrim, Inc., CCD camera has 16 has rectangular pixels. A CCD camera with square pixels would simplify the calculating procedures.

Alternatively, a 3-chip CCD camera **20**, indicated in phantom in FIG. **1***c*, may be used to reimage the slides of the region of interest. The CCD camera **20** provides digitized images for subsequent analysis by the computer **12**. Broad bandpass filters, which are part of the CCD camera **20**, produce a representation of the lesion as a set of three narrowband images. The filters are typically in accordance with CIE Standard Observer, wherein the bandwidths are broad.

FIG. **2** is a schematic illustration of the illumination and imaging portions of a preferred computer controlled imaging system **22** in accordance with the present invention, for imaging a region of interest of skin including a lesion. The electronic camera **23** may be a 10-bit monochromatic electronic CCD camera **23**, such as the Xillix Model 1400, available from Xillix Technologies Corp., Canada. The Xillix camera is equipped with wide band, low distortion foreoptics, such as the XJP 1.9/0501, available from Jos. Schneider Werke, Germany. The lower distortion fore optics and the camera minimize chromatic aberrations of the optical system over the "multispectral" sequence of exposures, enabling registration of images with sub-pixel accuracy, over the entire field of view.

To ensure repeatability of imaging conditions and to minimize required intervention by the operator, it is preferred that the system be operated at a preset f/stop. For cameras such as the Xillix Model 1400, exposure times are preferably controlled by the computer **12** through an electromechanical shutter that can operate reliably between minimum and maximum exposure times t_{min} and t_{max}.

The imaging system provides low-noise, high-resolution digital images at high data transfer rates, with low distortion imaging over the entire range of wavelengths covered by the collection of filters. The Xillix camera, discussed above, has a resolution at the skin surface of about 20 microns per pixel.

The CCD camera **23** is preferably contained in a hand-held unit, represented schematically as box **24**. The illuminator source **25** is a tungsten-halogen lamp whose intensity is controlled by a light-stabilized power supply **26** whose setting is automatically adjusted by the computer **12**. A 150 watt lamp, such as the Phillips EJA, available from Phillips Electronics North America Corporation, N.Y., may be used, for example. The output of the lamp **25** is white light A narrowband filter **27** is provided between the source and an optical fiber **28**. A plurality of narrowband filters, each one corresponding to a different spectral wavelength band, are mounted on a filter wheel **29**. Preferred filter bandwidths are listed in Table 1, below. The filter wheel **29**, which is driven by a stepping motor **29***a*, advances each filter to its proper position between the lamp **25** and the optical fiber **28**, and holds each filter in position for a sufficient period of time. The computer **12** controls the motor **29***a*. More or fewer filters may be used. Appropriate lenses **14** are provided between the lamp **25** and the filter **27**, and between the filter **27** and the optical fibers **28**, as well. One or more fiber illuminators are provided for conveying the light from the source to the lesion. Two such illuminators **30***a*, **30***b* are shown in FIG. **2** for simplicity. Although the fiber illuminator illustrated is a bifurcated pair, a ring illuminator which provides more nearly uniform illumination at the skin surface, is preferred. An angle of illumination of about 20° is also preferred. A Fostec Model A0603 available from Fostec, Inc., N.Y., may be used, for example.

The hand-held portion of the system **24** of FIG. **2**, which includes the camera **23**, may be mounted on a cantilevered arm (not shown) that can be locked into position.

The digital signals making up each of the digital images output from the camera **23** are provided to the computer **12**. The computer **12** conducts image processing procedures on the digital images to calibrate the images, and to objectively segment, estimate parameters, and classify the lesions based on the estimated parameters. Operator judgment is not required at any point in the process.

Control is maintained by the computer **12** over source intensity, filter position, and such camera settings as shutter timing, through the digital interface **12***a*. Key control parameters are empirically chosen on the basis of feedback from histograms of trial images. The intensity of the lamp **25** may be maintained at a stable value, commensurate with the 10-bit dynamic range of the camera **26**, by monitoring a secondary light source, connected electrically in series with the primary light source **25**. The light output from the secondary source is monitored by a light sensor that is optically isolated from light reflections associated with the primary source. Such reflections may be caused by the filters that are located on the filter wheel, or from the housing of the primary light source. This method provides optical feedback which is sensitive to changes in light intensity caused by changes in lamp lead resistance, for example, while it is insensitive to the variable amounts of light reflected from the filters, for example. By means of a closed control loop, the optical feedback from the secondary source is used to maintain long-term constant light output from the primary source.

The apparatus of FIG. **2** can be used for either clinical imaging of the skin, wherein the skin is imaged directly, dermoscopic imaging, wherein a layer of oil is provided over the skin and a layer of glass placed over the oil layer, or polarized imaging, where a polarizer **31** is added to minimize specular reflection as shown in FIG. **2**. In dermoscopic imaging, the index-matching oil sufficiently reduces the specular reflection to avoid the need for a polarizer.

Instead of being positioned between the light source **25** and the optical fiber **28**, the narrow bandpass filters **27** may be placed between the skin and the CCD camera **23** to filter the light reflected, scattered and radiated from the skin **2**.

The front end of the system preferably consists of a flat glass plate (not shown) for being placed over the skin. Light pressure is applied through the glass, onto the skin, throughout the imaging process. This helps to stabilize the region of

interest against unwanted motion which could blur an image or which could lead to spatial misregistration between images obtained in different filter bandpasses.

The preferred filters **27** for lesion imaging with a tungsten-halogen white light source **25** have the center wavelengths λ_i and bandwidths (FWHM) listed in Table 1, for i=1,2, . . . , M, M=10, wherein the bands are labeled by j=i−1=0,1, . . . M−1. Such filters are available, for example, from Intor, Inc., Tucson, Ariz. In each band, the exposure time is preferably selected to avoid saturation of the detector elements of the CCD camera **23**, as well as to maximize the linear dynamic range over which the image data are recorded. These exposure times should be constrained to be within limits t_{min} and t_{max} which are related to the electro-mechanical design of the shutter, optical throughput of the camera **23**, and avoidance of image blur associated with motion during the exposure sequence. Suitable values of t_{min} and t_{max} could be 10 ms and 550 ms, respectively, for example. The choice of center wavelength and FWHM for the filter channels, as well as the corresponding exposure times, should preferably also take into account the following considerations:

(a) The center wavelength and FWHM for at least two channels should be chosen so that characteristic absorption lines can be differentiated, such as those associated with melanin and hemoglobin;

(b) For a given set of center wavelengths, there are upper limits on the associated bandwidths if spectral independence of data in different channels is to be maintained, as illustrated in FIG. 1(*a*);

(c) Bandpasses should be chosen in the red, green and blue portions of the spectrum which enable "true-color" reconstruction of skin images that are suitable for visualization by clinicians;

(d) The need for high signal-to-noise ratio in each image sets practical lower limits on the product of exposure time and filter bandwidth, especially at short wavelengths, where detector response falls off and lesion reflectance is low; and

(e) The total time taken to acquire the images in all filter bands is preferably less than about three minutes, to minimize patient discomfort and possible motion.

Based on considerations (d) and (e) above, and also taking into account the varying spectral reflectances of skin of different colors, the exposure times in each filter channel are preferably adjustable, with settings based on the dynamic range achieved on an empirical basis, with trial images. In this manner, both dynamic range and signal-to-noise ratio can be maximized for each filter channel. The preferred method is to choose t_{expi} by iteration, based on intensity histograms of images of the skin obtained with trial exposures at each wavelength band. The histograms are analyzed to determine the number of pixels at the saturation intensity level, $I_{sat}=2^b-1$ (1023 for b=10 bits). The exposure time is decreased if the number of saturated pixels exceeds a predetermined amount, such as 0.01% of the total. Conversely, to maintain high signal-to-noise ratio, the exposure time is increased if a predetermined percentile in the histogram, 99.9%, for example, is reached at less than a preset threshold, such as 99.5% of I_{sat}. The iteration process typically converges after two or three trials.

The preferred exposure times at each wavelength for imaging skin of different colors to classify melanomas are listed in Table 1, for the embodiment of FIG. **2** with 10 filters. It has been found that for the blue channel centered at 450 nm, the optimal exposure time for dark skin is 273 ms, which is more than double the optimal 107 ms exposure time for light skin. On the other hand; in the near infrared channel centered at 780 nm, the exposure times listed are much shorter, between 24 and 35 ms, and vary relatively little with skin type. The optimal exposure time for dark skin in the deep blue channel at 430 nm is at t_{max}=550 ms, due to the low skin reflectance and relatively low optical throughput of the system at this short wavelength. Even with an exposure time this long, therefore, the image is less than fully exposed. Greater throughput at this wavelength could be achieved, at the expense of poorer response in the infrared.

In Table 1, the FWHM at 450 nm, is 100 nm, which is much broader than for other wavelengths. It has been found that where images are desired for visual analysis as well as computer processing, the broad wavelength band at 450 nm more closely matches the blue response of the human eye and is therefore preferred. In addition, the broad wavelength band provides data at a higher signal-to-noise ratio.

Table 1 appears below:

Optimal Exposure Times (msec) vs. Skin Color

Filter Number (j = i − 1)	Center Wavelength (nm)	Filter FWHM (nm)	Very Light Skin	Medium Skin	Tan Skin	Dark Skin
0	430	60	405.2	436.5	484.4	550.0
9	450	100	106.8	124.9	156.1	273.3
1	500	40	56.4	62.9	88.7	130.7
2	550	10	44.2	50.4	71.3	92.9
3	600	10	19.1	24.0	29.6	39.2
8	650	10	74.5	92.3	104.9	132.0
4	700	10	71.6	86.0	98.0	114.4
5	780	30	25.8	29.1	34.9	23.6
6	880	50	34.1	38.6	44.8	46.1
7	950	60	161.1	187.6	205.8	212.0

Tables similar to Table 1 can be readily constructed based on experimental results for other applications, where other spectral bands may be better suited. For example, in the analysis of wound healing, the ability to distinguish oxygenated from deoxygenated blood would be desirable. In addition, the wavelengths and exposure times in Table 1 reflect a balance between the best results for subsequent analysis of the images by a computer, and the best results for visual observation of the images. If visual observation is not necessary, other wavelength bands and exposure times may be used.

FIG. 3(*a*) describes how the systems and methods of the present invention provide for calibration of the recorded images. The calibration procedure permits 10-bit image data to be recorded over a large linear dynamic range in each spectral band, independent of skin type. The recorded images can also be standardized for diffuse spectral reflectance. Consistent measures of reflectance ratios in different spectral bands can therefore be obtained, despite variations in illumination pattern with wavelength, changes in the position of the illuminator, or aging of the lamp, for example.

First, the effects of dark current and "fixed pattern noise" are removed in Step 1. N images are recorded by the camera without illumination. Preferably 8 such dark images are recorded. The average of these N dark images, ID is calculated and stored in the computer **12**.

Second, spatial inhomogeneities in the illumination and in the response associated with each CCD pixel are removed in Step 2. A sequence of N' images of an illuminated flat, diffuse reflectance standard, such as a white Spectralon®

target (R>99%) recorded. As above, N' is preferably 8. The N' images are recorded at each wavelength band. To average over local inhomogeneities in the reflectance standard, the target is moved continuously during the integration time and between exposures. A small motor, such as a reciprocating motor, may be used. The integration time and/or lamp intensity are adjusted by the computer **12** at each wavelength band until negligibly few of the pixels are at or just below an intensity level corresponding to saturation. These N' "flat-field" images are averaged to reduce the effect of spatial non-uniformities in the reflectance standard, as well as to improve the detection signal-to-noise ratio. The resulting averages are stored in the computer as I_{wi}, where i=1, 2, . . . M.

Next, monochromatic "raw data" images of the skin, I_{si}, are captured by the camera and digitally acquired by the computer **12** within each filter passband, i=1,2, . . . M. If dermoscopic imaging is used, where a thin layer of mineral oil is spread between the skin and a cover glass is fixed in position in front of the camera, each image of the skin preferably contains an image of a narrow strip of oil-free, diffusely reflecting gray material, held in place on the inside surface of the cover glass, and located along one edge of the field of view. The material may be cut out of a Kodak "18% gray" card. Dermoscopic imaging is preferred for melanocytic lesions. The alternative clinical imaging mode is preferred for the imaging of wounds and burns because contact with the wound or burn by a cover glass is not desired. Although FIG. **2** indicates a lesion present on the skin **2**, it will be readily understood that the same method will apply when a wound or burn is present, instead. In the clinical imaging mode, it is preferable to reduce specular reflections by employing the polarizer **31**, as indicated in FIG. **2**.

In either the dermoscopic or clinical imaging techniques, a fourth step is preferably provided, in which the raw data is compensated for dark current and fixed pattern noise and then normalized to the flat-field images. The dark-field compensation is performed by subtracting the stored average dark image I_D both from the flat-field image I_{wi} and from the raw data image I_{si}. The ratio of the results of these subtractions is then taken. This standardizes the dark-corrected raw data to the flat-field image, compensating for spatially varying illumination and pixel-to-pixel response variations. After the ratio is taken, the result is standardized to the maximum level, 2^b-1 which equals 1023 where b=10 in a 10-bit data representation. The normalization process thus converts the image of the skin and the gray strip into a standardized diffuse reflectance map, with the result preserving a large linear recording dynamic range. In FIG. **3**(*a*), the dark-field corrected and flat-field-normalized images, also referred to as "flat-field-calibrated" images, are denoted as I_{si}. In any image, standardization to maximum level can be reinterpreted directly in terms of equivalent diffuse reflectance on the basis of the average gray level over the image of the gray strip, <Igray strip>$_i$ and the measured average diffuse reflectance of the gray strip, which is approximately 0.2 and varies in a known and repeatable manner with wavelength.

Preferably, the average image intensity in the gray-strip region is also used to calculate weighting factors for combining three or more monochromatic images to provide "true-color" visualizations of lesion images on the computer **12** and display **19**. This is preferably accomplished in Step **5**, where the user selects the spectral bands to be used in the color visualization. Step **5** can take place prior to the imaging session. Four bands are currently preferred for such visualization. Filter bands j=3 and 8, in a 3:2 ratio, for the red (R) channel, filter band j=2 for the green (G) channel, and filter band j=9 for the blue (B) channel, in Table 1. As indicated in Step **6** of FIG. **3**(*a*), the relative weights applied to the R:G:B channels are preferably inversely proportional to <Igray strip>$_i$ the average intensity over the portion occupied by the gray strip area in each image. This procedure tends to reconstruct the hues and saturations in the original scene to within accuracy limits associated with response nonlinearities of the display **19**. To minimize the effects of such nonlinearities with display monitors such as the Sony Model GDM-175E1 Multiscan monitor, for example, the viewer may prefer to adjust the maximum brightness in the image to correspond to the maximum image intensity level of the monitor. A linear transformation step, which can be readily accomplished by commercial software such as Adobe Photoshop, may be used. If the digital images are derived from photographic slides, as in the embodiment of FIG. **1**(*c*), steps **5** and **6** are not necessary.

As indicated by dashed lines in FIG. **3**(*a*), either the normalized monochromatic images resulting from Step **4** or the color visualization provided from Step **6** can be displayed on the display **19**. Any or all of the monochromatic raw images could be displayed as well.

FIG. **3**(*b*) is a flow chart of a preferred method of processing images according to the present invention for characterizing the condition of a region of interest of the skin of a subject which includes a skin lesion. A skin lesion is selected at Step **50**. Digital images of the lesions illuminated by light filtered at the desired wavelengths of λ_1–λ_4. . . , are digitally recorded in Steps **52**, **54**, **56** and **57**. . . , as described above. Each of these digital images is processed separately. In Step **58**, the image taken at the lowest wavelength band is used to create a mask for segmentation. At Steps **60**, **62**, **64**, **65** . . . , each of the images of the lesion that correspond to different wavelengths are segmented by means of the segmentation mask obtained at Step **58**. Lesion parameters are computed from each of the segmented images, in Step **66**. Lesion parameters found to be useful for classifying and characterizing the lesion and statistical methods for computing the estimated values of the parameters, are discussed further, below. The estimated values of the parameters are provided to a linear classifier in Step **68**. The linear classifier employs a linearly weighted sum of the individual parameters to derive a value used to classify the lesion as malignant or benign. A non-linear classifier such as a Gaussian quadratic classifier or an artificial neural-net classifier, each employing a suitable defined merit function, may be used as well. In either case, the numerical value produced by the classifier is subjected to a threshold test at Step **100**, such that if the test is passed, the lesion is suspected to be malignant melanoma. If the test is failed, the lesion is declared not to be melanoma. The lesion could also be characterized as invasive or non-invasive with a different classifier.

I. SEGMENTATION

The segmentation algorithms will now be described. The function of the segmentation algorithms is to discriminate between the lesion and normal skin in the field-of-view of the imaging device. This is a complex function since not only is the lesion appearance highly variable but so is the appearance of healthy skin due, for example, to the presence of blotches, hair, wrinkles, etc. The automatic algorithm described here is based on the images in the blue spectral band, from about 400 nanometers (nm) to 500 nm. This spectral band was selected because melanin absorption

increases rapidly as the wavelength decreases. While the use of ultraviolet radiation could be advantageous, since ultraviolet radiation is carcinogenic, only low doses can be used.

Segmentation in blue consists of several automatic steps:

Location of major peaks in the histogram

First, the histogram of intensity levels in the whole image is determined. Then, given a sliding window with the range of $(2I_r+1)$ intensity levels, the number of peaks N_p in the histogram over that range is determined. If $N_p<2$, the range is decreased by two levels and if $N_p>3$, the range is increased by two levels and the process is repeated until $N_p=2$ or 3. For most of the images in the data base used in this study, there are two major peaks in the histogram. Examples of such histograms are shown in FIG. **4**(*a*) for a malignant melanoma and in FIG. **4**(*b*) for an atypical melanocytic nevus. The lesions correspond to the lower intensity peak, since it is darker than the surrounding skin due to strong absorption by melanin at 400 nm. However, some lesions are quite inhomogeneous, and the automatic procedure described can find 3 major peaks, as illustrated in FIGS. **5**(*a*) and **5**(*b*).

Location of the intensity threshold

If two major peaks are found in the intensity histogram, then the threshold value I_{th} is selected to be at the histogram minimum between these two peaks, as indicated in FIGS. **4**(*a*) and **4**(*b*). In the case of three peaks, it has been found that, if the middle peak is closer to the lowest intensity peak, the threshold value is at the minimum between the middle and the highest intensity peak. If the middle peak is closer to the highest intensity peak, then the threshold value is at the minimum between the middle and the lowest intensity peak, as shown in FIGS. **5**(*a*) and **5**(*b*).

Iterative thresholding of the image

The next step in image segmentation is iterative thresholding of the images. Given the intensity threshold value, image thresholding has been typically accomplished as follows. The intensity I(x,y) of a pixel at location (x,y) is set to zero if it exceeds I_{th}, i.e.,

$$I_L(x, y) = \begin{cases} I(x, y), & \text{if } I(x, y) < I_{th}; \\ 0, & \text{otherwise.} \end{cases} \quad (1)$$

FIGS. **6**(*a*) and **6**(*d*) are examples of digital images of malignant melanoma and atypical melanocytic nevus in the blue spectral band, respectively. FIGS. **6**(*b*) and **6**(*e*) are images resulting from the direct thresholding as in Eq. (1). As shown in FIGS. **6**(*b*) and **6**(*e*), "holes" can appear within the lesion. Therefore, an iterative approach is preferably used. First, the intensity of pixels at the image edges is set to zero. Then as each iteration proceeds, the intensity I(x,y) of a pixel at location (x,y) is set to zero if it exceeds I_{th} and at least one of its nearest neighbors has zero intensity, i.e.,

$$I_L(x, y) = \begin{cases} 0, & \text{if } I(x, y) \geq I_{th} \text{ and } N_{nn} = 0; \\ I(x, y), & \text{otherwise,} \end{cases} \quad (2)$$

where

$$N_{nn}=\min[I(x-1,y),I(x+1,y),I(x,y-1),I(x,y+1),]. \quad (3)$$

This procedure is iterated until there are no pixels with $I(x,y)\geq I_{th}$, and a nearest neighbor with zero intensity. Typically, only a few iterations are required to complete this step. The resulting images are shown in FIGS. **6**(*c*) and **6**(*f*).

FIGS. **7**(*a*) and **7**(*d*) are other examples of digital images of malignant melanoma and atypical melanocytic nevus, respectively. FIGS. **7**(*b*) and **7**(*e*) are images resulting from the iterative thresholding described above. Various dark blobs are seen in the images outside of the lesion area. These are removed in the following step.

Image cleaning

Some of the blobs in the thresholded images arise naturally due either to dark spots on the normal skin or to hair as in FIG. **7**(*b*). Others are artifacts such as the film edge at the top of the nevus image in FIG. **7**(*e*), or dark bands at the image edges from the slide mounts. These bands are removed by automatically testing for their presence and then setting the intensity of appropriate pixels to zero. The remaining blobs could also be removed by determining the overall number and size, i.e., number of pixels, of connected blobs, and then setting to zero the intensity of pixels belonging to the small ones. However, since the size of some lesions exceeds 100,000 pixels, this would be computationally very intensive. Therefore, in practice, this step is preferably carried out as follows. First, perimeter pixels for all blobs in the image are located. The number of such pixels is typically less than 10,000. Then, each of these perimeter pixels is assigned to a unique blob and its size, the number of perimeter pixels in the blob, is determined. The intensities of pixels belonging to blobs of size less than 30% of the maximum size for that image are set to zero. This process is iterated until all the small blobs are removed. Typically less than 10 iterations are needed. The intensity of all the nonzero pixels is then set to 1. The resulting binary lesion mask has the following property:

$$I_B(x, y) = \begin{cases} 1, & \text{if pixel at } (x, y) \text{ belongs to lesion;} \\ 0, & \text{otherwise.} \end{cases} \quad (4)$$

FIGS. **7**c) and **7**(*f*) illustrate the resulting lesion masks.

In the images illustrated in FIGS. **7**(*a*) and **7**(*d*), dark hairs were either absent or were not adjacent to the lesion. However, there are many images with prominent dark hair overlapping lesions. Segmentation of such images is described in the following section.

Segmentation of images in presence of hair

FIGS. **8**(*a*) and **8**(*e*) are examples of lesion images with hair. Since the segmentation algorithm described in the previous section would leave some of these dark hairs connected to the lesion, images with hair require special preprocessing to allow for hair removal from the normal skin. Since hair is a problem because of its high contrast with respect to the normal skin in the blue, a spatial filter was designed to locate hairs. This filter, shown in FIG. **9**, is magnification dependent. It is applied to every pixel of the original image and the result is thresholded at the 5% of maximum value in the whole filtered image. The filtered images are shown in FIGS. **8**(*b*) and **8**(*f*) in reverse intensity contrast, wherein bright features are dark. Hairs are clearly located in the filtered images. It should be noted that the lesion interior is almost entirely blank, indicating poor contrast between hair and lesion.

Hairs are removed by an averaging process. For every non-zero pixel at (x,y) in the filtered image one finds the locations of 4 nearest pixels (x_l, y), (x_u,y), (x, y_l), (x,y_u) (where $x_l<x<x_u$ and $y_l<y<y_u$) with zero intensity. Then the intensity of every pixel in the original image that has

non-zero intensity in the filtered image is replaced as follows:

$$I_n(x, y) = \frac{1}{12}\sum_{k=1}^{3}[I(x_u + k, y) + I(x_l - k, y) + I(x, y_u + k) + I(x, y_l - k)]. \quad (5)$$

The images averaged in this way are shown in FIGS. **8**(*c*) and **8**(*g*). It is seen that the contrast between hairs and normal skin is considerably reduced in these images. After this preprocessing, the segmentation algorithm described in the previous section is applied to the averaged image. The final binary lesion masks are shown in FIGS. **8**(*d*) and **8**(*h*).

The preprocessing step described above may be used for all lesion images, regardless of the presence of hair, enabling fully automated lesion segmentation. However, since this requires more computation and causes some border blurring, the need for preprocessing due to the presence of dark hair is preferably indicated interactively by an operator, and images preprocessed only when necessary.

Segmentation of images in other spectral bands

Since melanin absorption is strongest in the shortest-wavelength band, the lesion area, which appears as a dark region in the image, appears largest in the blue spectral band. Since longer wavelength radiation penetrates deeper into skin, if the thickness of the melanin-containing layer compensates for the weak absorption, that part of the lesion will appear dark even in the red spectral band. For thick melanomas, with Breslow thickness greater than 1 mm, one expects dark lesions even m the infrared bands. This was observed, for example, by Marchesini et al., Photochemistry & Photobiology, "In vivo spectrophotometric evaluation of neoplastic and non-neoplastic skin pigmented lesions. III. CCD camera-based reflectance imaging," Vol. 62, 1995, pp. 151–154. However, for early malignant melanomas, with Breslow thickness less than 1 mm, great variability of images in the red spectral band has been found. There may be so little contrast between the lesion and the normal skin that direct segmentation is not possible. Therefore, segmentation of lesion images in all spectral bands with wavelength λ uses the binary lesion mask of Eq. (4), obtained in the shortest-wavelength band, here blue, i.e.,

$$I_L(x,y;\lambda) \equiv I(x,y;\lambda) \times I_B(x,y) \quad (6)$$

FIGS. **10**(*a*)–**10**(*f*) are a series of images of the lesions, with their corresponding histograms shown in FIGS. **5**(*a*) and **5**(*b*), segmented in the blue, green, and red spectral bands, as indicated. The automatically determined lesion borders are superimposed on the original lesion images. The area of dark regions is largest in the blue.

II. LESION PARAMETER ESTIMATION

Objective and automatic lesion classification requires quantitative algorithms for lesion parameter estimation from their segmented images. Such parameters should be dimensionless, independent of lesion location and orientation in the image, and of the overall image brightness. It is convenient to separate the parameters used here into four broad classes: asymmetry, blotchiness, border, and texture. Parameters with the highest diagnostic accuracy for malignant melanoma are listed in FIG. **11**, together with the values of diagnostic accuracy, sensitivity, and specificity, for a training set of images of 41 malignant melanomas and 104 atypical melanocytic nevi obtained with the imaging system described above, with respect to FIG. **1**(*a*) wherein the monochrome camera **16** was used to digitize slides. The subscript r, g, or b refers to the red, green, or blue spectral band in which the parameter is evaluated. If additional spectral bands are used, then each of the parameters could be computed at the additional spectral bands, as well.

Specific algorithms for these parameters are described below. For simplicity it is assumed that the image pixels are square but the algorithms described below may be implemented for rectangular pixels as well.

Lesion Asymmetry

Asymmetry parameter

The lesion asymmetry parameter is based on moments of the intensity distribution. First, the lesion orientation angle θ is used to locate the principal axes, which are just the symmetry axes for symmetric lesions. The angle θ is computed from

$$\tan 2\theta = \frac{2\langle (x - x_c)(y - y_c)\rangle}{\langle (x - x_c)^2\rangle - \langle (y - y_c)^2\rangle}, \quad (7)$$

where the lesion intensity centroid is at

$$x_c = \langle x\rangle \text{ and } y_c = \langle y\rangle. \quad (8)$$

The angular brackets in Eqs. (7) and (8) denote an intensity moment, which for any function f(x,y) of position in the image can be computed as follows:

$$\langle f(x, y)\rangle \equiv \frac{\sum_x \sum_y f(x, y) I_L(x, y)}{\sum_x \sum_y I_L(x, y)}, \quad (9)$$

where $I_L(x, y)$ is the segmented lesion image. In order to compare properties of different lesions, the parameters used are independent of the orientation of the lesion in the image. Therefore, the lesion asymmetry is determined with respect to the principal axes. The measure of asymmetry described here requires rotation of the image by an angle θ so that principal axes are parallel to the image axes. In this principal-axis coordinate system the following asymmetry factors are defined:

$$A_x = \frac{\sum_n \sum_y |I_L(x_c + n, y) - I_L(x_c - n, y)|}{\sum_x \sum_y I_L(x, y)}, \quad (10a)$$

$$A_y = \frac{\sum_x \sum_n |I_L(x, y_c + n) - I_L(x, y_c - n)|}{\sum_x \sum_y I_L(x, y)}. \quad (10b)$$

The asymmetry parameter,

$$A = A_x + A_y, \quad (11)$$

is a measure of asymmetry in the geometric shape of a lesion as well as in the distribution of lesion pigmentation. Asymmetry parameters tend to be larger for malignant melanomas than for atypical melanocytic nevi.

Binary asymmetry parameter

If the intensity distribution I_L in Eqs. (10a) and (10b) is replaced by the binary intensity distribution of Eq. (4), then the corresponding asymmetry parameter A_{bin} is the fraction of the lesion pixels which do not have a counterpart on the

other side of the principal axis. Thus, when based on the binary intensity distribution, parameter A_{bin} is a measure of the asymmetry of the geometric shape of the lesion.

Lesion Blotchiness

Visually, many early malignant melanomas appear blotchy. In multispectral images there may be darker and lighter regions or blotches of rather homogeneous intensity. In color images, in contrast, there may be regions of different colors. Therefore, it is of interest to quantify such blotchiness in order to differentiate malignant from benign lesions.

Blotchiness Parameter Based on Spatial Intensity Distribution

The lesion is divided into N_t "topographic" regions. If I_{max} and I_{min} are the maximum and minimum intensities in the lesion in some spectral band, respectively, then a pixel at (x,y) belongs to the nth region if

$$I_{\min} + (n-1)\frac{I_{\max} - I_{\min}}{N_t} \le I_L(x, y) < I_{\min} + n\frac{I_{\max} - I_{\min}}{N_t}. \quad (12)$$

For nth topographic region defined in Eq. (12), a distribution of distances of pixels in that region from the intensity centroid of the binary lesion mask

$$d_n(x, y) = \sqrt{(x_n - x_c)^2 + (y_n - y_c)^2} \quad (13)$$

is obtained and its mean value $<d_n>$ and variance $Var(d_n)$ are computed. The measure of lesion blotchiness based on spatial intensity distribution is

$$Bl = \frac{\sum_{n=1}^{N_t} \sqrt{\mathrm{Var}(d_n)}}{\sum_{n=1}^{N_t} \langle d_n \rangle}. \quad (14)$$

This parameter can be evaluated in every spectral band.

Blotchiness Parameter Baled on Centroids

The lesion is again divided into N_t "topographic" regions as defined in Eq. (12). An intensity centroid $(x_c(n),y_c(n))$, defined in Eqs. (8) and (9), is then computed for each such region separately. The blotchiness parameter based on the centroid is defined as

$$C=(X_{max}-X_{min})(Y_{max}-Y_{min})/A_l \quad (15)$$

where, for example, X_{max} is the maximum value of $x_c(n)$, and A_l is the lesion area in pixels. This blotchiness parameter is also determined in each spectral band separately.

Blotchiness Parameter Based on Spatial Color Distribution

The "color" in this analysis is not related to the visual perception of color. It is a quantitative descriptor of the relative intensities in red, blue, and green channels in a particular pixel.

All the other lesion parameters described here involve analysis of images in each spectral band separately. Therefore, absolute calibration of image intensities was not necessary. However, in order to describe the color distribution, normalization of intensities in red, green, and blue spectral bands is needed, so that intensities in the three channels are equal for white. In the spherical color coordinate system,

$$R(x, y) = \frac{I_R(x, y)}{I_R(x, y) + I_B(x, y) + I_G(x, y)}, \quad (16)$$

$$G(x, y) = \frac{I_G(x, y)}{I_R(x, y) + I_B(x, y) + I_G(x, y)},$$

where the subscripts R, G, B refer to red, green, and blue spectral bands, are chosen as the independent variables. The lesion is then divided into color regions as follows. First R(x,y) and G(x,y) are divided into N_R and N_G topographic regions. A color region is defined as a particular combination of two topographic regions. The total number of color regions is

$$N_C = N_R \times N_G. \quad (17)$$

The blotchiness parameter based on color is defined in analogy with Eq. (14):

$$Cl = \frac{\sum_{n=1}^{N_C} \sqrt{\mathrm{Var}(d_n)}}{\sum_{n=1}^{N_C} \langle d_n \rangle}. \quad (18)$$

Lesion Border

Border Irregularity Parameter

Border irregularity is a well-known feature of malignant melanomas. It is typically defined as the ratio of the measured lesion perimeter to the perimeter of a circle with the same area as the lesion. Since perimeter is difficult to estimate reliably, a statistical descriptor of border irregularity is used here. In addition, many lesions are elongated and an ellipse is a better approximation for such lesions with regular borders than a circle.

Using the binary lesion mask of Eq. (4), the lesion intensity centroid from Eq. (8), orientation angle from Eq. (7), area, and the aspect ratio defined as

$$AR = \frac{\sqrt{\langle x' - x_c)^2}}{\sqrt{\langle y' - y_c)^2}}, \quad (19)$$

where primes refer to the coordinate system defined by the lesion principal axes, are determined. These values are then used to construct an ellipse that is the best regular approximation to the lesion border. For each lesion border pixel at (x_b,y_b), its angle with respect to the horizontal axis:

$$\phi = \tan^{-1}\frac{(x_b - x_c)}{(y_b - y_c)}, \quad (20)$$

and the location of the ellipse border for the same angle $(x_e(\phi)y_e(\phi))$ are determined. The distribution of distances between the ellipse border and lesion border:

$$d_{eb}(x_b,y_b)=d_b(x_b,y_b)-d_e(\phi), \quad (21)$$

where

$$d_b(x_b, y_b) = \sqrt{(x_b - x_c)^2 + (y_b - y_c)^2} \quad (22)$$

and

$$d_e(\phi) = \sqrt{x_e^2 + y_e^2}, \quad (23)$$

is obtained and the border irregularity parameter is defined as

$$B = \frac{\sqrt{\mathrm{Var}(d_{eb})}}{\langle d_b \rangle}. \quad (24)$$

Border Gradient Parameter

Another parameter that quantitatively characterizes lesion border is the measure of intensity gradients across the lesion borders over the length scale defined by n_g, in units of pixels. For each lesion border pixel at (x_b,y_b) one determines whether pixels at $(x_b \pm n_g, y_b \pm n_g)$ are at the border. If they are not, then the gradient is defined as

$$G(x_b,y_b)=\tfrac{1}{2}[|I(x+n_g,y)-I(x-n_g,y)|+|I(x,y+n_g)-I(x,y-n_g)|]; \quad (25a)$$

otherwise, if pixels at $(x \pm n_g, y)$ are not on the border,

$$G(x_b,y_b)=|I(x+n_g,y)-I(x-n_g,y)|, \quad (25b)$$

or, if pixels at $(x, y \pm n_g)$ are not on the border,

$$G(x_b,y_b)=|I(x,y+n_g)-I(x,y-n_g)|. \quad (25c)$$

The border gradient parameter is defined as

$$G = \frac{\sqrt{\mathrm{Var}(G)}}{\langle G \rangle}. \quad (26)$$

Lesion Texture

The description of lesion texture is particularly vulnerable to subjective judgement. The quantitative evaluation of lesion texture parameters is possible only using computer-based image analysis. While many such parameters are possible, those found to be helpful in discriminating between malignant melanomas and atypical melanocytic nevi are described below.

Texture Parameters Based on Local Intensity Variations

Texture parameters are defined over a length scale n_t in units of pixels. For example, consider a pixel located at (x,y) in the lesion. Let I_l and I_u be the minimum and the maximum intensities in an image in the $2n_t+1 \times 2n_t+1$ window around this pixel, i.e., in the range $[x-n_t, x+n_t]$ and $[y-n_t, y+n_t]$. Consider a variable

$$C_1(x, y) = \frac{I_u - I_l}{I_l}. \quad (27)$$

The first two texture parameters are defined as:

$$T1 = \frac{\sqrt{\mathrm{Var}(C_1)}}{\langle C_1 \rangle} \quad (28)$$

and

$$T2 = \sqrt{\mathrm{Var}(C_1)} \quad (29)$$

Another texture parameter uses the following variable:

$$C_3(x,y)=4w(0,0)+w(-n_t,0)+w(n_t,0)+w(0,-n_t)+w(0,n_t) -2[w(-n_t,-n_t)+ w(-n_t,n_t)+w(n_t,-n_t)+w(n_t, n_t)] \quad (30)$$

where

$$w(i,j)=I(x+i,y+j)/I(x,y). \quad (31)$$

If the value of C_3 is negative, it is set to zero and the corresponding texture parameter is

$$T3 = \frac{\sqrt{\mathrm{Var}(C_3)}}{\langle C_3 \rangle}. \quad (32)$$

Another variable that leads to a texture parameter useful for classification of melanocytic lesions is:

$$C_4(x,y)=8w(0,0)-w(-n_t,0)-w(n_t,0)-w(0,-n_t)-w(0,n_t) -w(-n_t,-n_t)- w(-n_t,n_t)-w(n_t,-n_t)-w(n_t,n_t) \quad (33)$$

Again, if the value of the variable is negative it is set to zero and the corresponding texture parameter is

$$T4 = \frac{\sqrt{\mathrm{Var}(C_4)}}{\langle C_4 \rangle}. \quad (34)$$

Texture Parameters Based on Pigmented Network

Texture parameters have also been developed by considering the properties of a pigmented network. These texture parameters are measures of variability in the area of the dermal papillae and in the aspect ratio (length/width) of the rete ridges.

Since dermal papillae appear as the brighter part of the network, one seeks all the local maxima over a $2n_t+1 \times 2n_t+1$ window. Starting from such a maximum at (x_m,y_m), one finds local one-dimensional minima in eight directions (2 vertical, 2 horizontal, and 4 diagonal) and locates the vertices of an octagonal region one pixel closer to the maximum intensity pixel than the minimum pixel. Such octagonal regions approximate the areas of dermal papillae A_{dp} which are computed from the known location of vertices; the corresponding texture parameter is

$$T5 = \frac{\sqrt{\mathrm{Var}(A_{dp})}}{\langle A_{dp} \rangle}. \quad (35)$$

Some of the areas determined by this algorithm are due to bubbles visible in some of these dermoscopic images. However, since there are typically on the order of hundreds of areas, and on the order of tens of bubbles, the statistical parameters should not be significantly biased by this artifact.

The aspect ratio of rete ridges is determined in a similar fashion, although one starts with local minima since rete ridges appear dark in the images. The vertices of an octagonal region are determined in this case from one-dimensional maxima in the eight directions. The maximum and minimum

extents of this region are then determined and the aspect ratio R is computed. This texture parameter then is

$$T6 = \frac{\sqrt{\mathrm{Var}(R)}}{\langle R \rangle}. \quad (36)$$

III. LESION CLASSIFICATION

Selection of lesion parameters for classification was done by determining the maximum diagnostic accuracy for malignant melanoma for each parameter computed in every spectral band available for the training set of images. As mentioned above, diagnostic accuracy, sensitivity to malignant melanoma and specificity for the selected twenty two parameters are shown in FIG. **11**. These parameters were then used as input to the linear classifier. Nonlinear classifiers may be used as well.

For each lesion k the linear classifier is

$$L(k) = \sum_{n=1}^{22} w_n X_n(k), \quad (37)$$

where $X_n(k)$ are the parameters for the kth lesion and weights w_n are to be determined so that a specified function F(L) attains maximum value. The following functions F(L) were used: 1) specificity under constraint of 100% sensitivity to malignant melanoma for the training set which included 41 malignant melanomas and 104 atypical melanocytic nevi; (2) classification accuracy for the 24 invasive and 16 noninvasive malignant melanomas of the training set; and 3) correlation with the Breslow thickness for the 24 invasive malignant melanomas.

Given any training set of lesion images and corresponding set of lesion image parameters, the weights that maximize F(L) are found as follows. First, an initial range and resolution Δ for w_n are selected. For each allowed set of values of w_n, the values L(k) are computed for each lesion. The value F(L) is determined based on the input from histopathological evaluation of the lesion based on a biopsy, such as the diagnosis of the lesion as benign or malignant, and the Breslow thickness for a malignant melanoma The range of w_n's is adjusted until the maximum value of F(L) is inside the range. Then the resolution Δ is reduced by a factor of two, and the process is repeated until Δ reaches specified minimum value Δ_{min}. This procedure determines the weights w_n only up to a multiplicative constant. It is noted that the classifiers resulting from a particular training set are applicable only to images with a specific spatial and spectral resolution, and that lesion images obtained with a different imaging system may require the development of different classifiers, by the procedures described above.

Since detection of melanoma in its early stage significantly improves prognosis, there is a need for reliable methods of early detection. Clinical evaluation of melanocytic lesions is, however, a problem since reliable differentiation between early malignant melanoma with Breslow thickness less than 1 mm and atypical melanocytic nevus is difficult even for experienced dermatologists. In order to detect as many early melanomas as possible, weights in the linear classifier are preferably chosen to maximize specificity under the constraint of 100% sensitivity to malignant melanoma for the training set. For each set of weights, one finds the threshold value L_{th} of the linear classifier such that a kth lesion is classified as suspicious of malignancy if $L(k) > L_{th}$, and as benign otherwise. The resulting classifier for the training set is

$$L_1 = 0.025A_{bin} + 0.090A_b + 0.069A_g + 0.160A_r + 0.128C_b + 0.095CI + 0.038B + 0.107T1_g + 0.064T2_g + 0.018T2_r + 0.111T3_b + 0.167T3_g + 0.268T5_b \quad (38)$$

where the weights are normalized so that the threshold value equals one. This classifier with sensitivity to malignant melanoma of 100% and specificity of 85% is shown in FIG. **12**. Statistical significance of the specificity and sensitivity was assessed by considering the binomial probabilities for the value of L_1 to exceed the threshold for the 41 malignant melanomas and 104 atypical melanocytic nevi of the training set separately. At the 95% confidence level, one finds that sensitivity is not less than 93% while specificity is not less than 79%. Since there are several melanomas very close to the threshold value, a practical classifier may use a threshold value that is less than one. It has been found that this set of 145 images is sufficient to yield statistically significant results. A greater number of images may be used, as well.

Some of the noninvasive melanomas, called melanomas in-situ, are confined to epidermis and are 100% curable by surgery. The invasive melanomas, i.e., superficial spreading melanomas in our data base, require more extensive surgery. Therefore, it is of clinical interest to differentiate between invasive and noninvasive melanomas and a linear classifier was trained to perform this task. This classifier, with weights chosen to maximize the over-all classification accuracy for the 24 superficial spreading melanomas and 16 melanomas in-situ of the training set is

$$L_2 = -1.00A_b - 0.14Bl_g - 2.47Bl_r - 0.4C_b - 0.98CI - 1.17T2_r + 0.53T4_b + 1.98T5_b + 1.58T6_b - 0.73 \quad (39)$$

where a constant was subtracted from the classifier values to obtain the threshold value of zero. This classifier, with overall classification accuracy of 92.5%, is shown in FIG. **13**.

Since prognosis for invasive melanomas correlates strongly with the Breslow thickness, a linear function of lesion parameters Q was trained to maximize the Pearson correlation co-efficient between Q and the Breslow thickness for a set 24 superficial spreading melanomas. This function is

$$Q = 0.955A_g - 1.391A_r + 2.791Bl_b - 1.320Bl_g + 0.146C_b + 0.267C_r - 0.506B + 0.202T1_g + 1.476T2_r - 0.485 \quad (40)$$

and is shown in FIG. **14**. Even though there are only 24 superficial spreading melanomas in the data base, the high correlation of 0.77 is statistically very significant since $p = 9 \times 10^{-6}$.

The classifiers of Eqs. (38)–(40) are applicable to the imaging system described above, with respect to FIG. **1**(*a*) wherein the monochrome camera **16** was used to digitize slides.

For other imaging systems, having different spatial and spectral resolution, different classifiers may need to be developed, based on a sufficient data base of lesion images obtained with that imaging system, in accordance with the procedures described above.

The segmentation, parameter estimation and classification programs described in Sections I–III, above, can be implemented on any personal computer, using a programming language, such as FORTRAN or C. The program can be stored on any convenient media readable by a computer, such as read only memory, ("ROM"), random access

memory with a battery backup, electrically programmed ROM (EPROM), electrically erasable ROM (EEPROM), floppy disc, CD ROM, or a hard disc. Other suitable media may be used, as well.

While the procedures of Sections I–III were described with respect to digital images obtained by imaging color photographic slides of skin lesions with a monochrome CCD camera **16** in accordance with the system of FIG. **1***c*, these procedures are readily adaptable to the analysis of digital images of skin lesions acquired directly from the region of interest of the skin with a monochrome CCD camera **6** of FIG. **1***a* and FIG. **2**.

In the process described in Sections I–III, above, segmentation was conducted in the blue wavelength band. The segmented mask in blue was then applied to images in the red and green wavelength bands. Where images at additional wavelengths are provided, segmentation is preferably first attempted at the shortest available spectral band where the contrast between the lesion and normal skin tends to be highest because of strong absorption by melanin. The segmented mask is then applied to the images in the remaining spectral bands. These steps are shown in FIG. **3***b*.

In addition, where parameters are described in terms of the red, green and blue wavelength bands in Section I–III, parameters can be derived at each of the other wavelengths used in the systems and methods above, in accordance with the procedures described in Section I–III. The additional parameters can be readily used to develop a classifier, also by the processes described in Section I–III.

The references cited above are incorporated by reference, herein.

While preferred systems and methods for practicing the present invention have been described above, it is understood that departures may be made from the systems and methods, without departing from the scope of the present invention, which is defined by the following claims.

We claim:

1. A method of characterizing a skin lesion wherein the absorption and scab of light in different spectral bands by the skin lesion is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging a portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital image by generating a single segmentation mask defining the boundary of the region of interest for each image, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the at least three spectral bands, without operator intervention;

automatically computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the portion of the region of interest determined by the segmentation mask, without operator intervention;

characterizes the condition of the skin as malignant or benign based on the estimated values, without operator intervention; and

outputs the characterization of the condition of the skin.

2. The method of claim **1**, further comprising estimating at least one value which is a function of the texture of the region of interest.

3. The method of claim **2**, wherein the computing step comprises estimating values which are statistical measures of local intensity variation in the digital images in each spectral band, which are a function of the texture of the region of interest.

4. The method of claim **2**, wherein the computing step comprises estimating values based on the ratio of standard deviation of the areas of dermal papillae to their mean within the segmentation mask.

5. The method of claim **2**, wherein the computing step comprises estimating values of the average and standard deviation of the thickness of rete ridges within the segmentation masks.

6. The method of claim **1**, further comprising estimating at least one value which is a function of the asymmetry of the region of interest in each spectral band, for two principal axes of the segmented image by:

determining the principal axes of the segmented image;

rotating the principal axes of the segmented image until they are oriented parallel to the coordinate axes of the image;

computing the differences in intensity between each pair of pixels whose locations, with respect to a principal axis, are mirror images of each other;

summing the absolute values of said intensity differences;

calculating asymmetry values with respect to each principal axis, by normalizing the said sum to the total intensity in the segmented images; and

adding together the asymmetry values calculated for the two principal axes.

7. The method of claim **1**, further comprising estimating at least one value which is a function of the blotchiness of the region of interest.

8. The method of claim **1**, further comprising estimating at least one value which is a function of the irregularity of the border of the region of interest by estimating a value which is a statistical measure of the deviation of the border of the segmentation mask from the border of an ellipse of the same area, aspect ratio, and orientation as the segmentation mask.

9. The method of claim **1**, further comprising estimating a value which is a function of the gradient at the border of the region of interest by estimating a statistical measure of the gradient values of the intensity of the digital images across the border of the segmented images, at each spectral band.

10. The method of claim **1**, further comprising characterizing the type of lesion as invasive or non-invasive.

11. The method of claim **1**, wherein the segmenting step comprises generating the segmentation mask from a digital image by:

removing digital signals from the digital image which correspond to hair structures;

deriving a threshold from a multimodal histogram of intensity levels;

iteratively applying the threshold to the digital signals of the digital image; and

removing digital signals which correspond to small blob-like regions from the masked image.

12. The method of claim **1**, wherein the digital imaging step further comprises digitally imaging the region of interest with a digital camera.

13. The method of claim **1**, further comprising:

photographing the region of interest with a color camera to form color photographic slides; and

illuminating the color photographic slides with light in each spectral band;

wherein the digital imaging step comprises digitally imaging the illuminated color photographic slides of the region of interest with a digital camera.

14. The method of claim 1, where the characterization step is based on a non-linear combination of the estimated values.

15. The method of claim 1, where the characterization step is based on a linear combination of the estimated values.

16. The method of claim 1, where the characterization step is based on a sequential combination of applying a linear combination of the estimated values and a non-linear combination of estimated values.

17. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least thee spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least tree spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a single segmentation mask defining the boundary of the region of interest for each image, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the at least three spectral bands;

computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the region of interest determined by the segmentation mask;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin.

18. The method of claim 17, wherein the estimating and characterizing steps are conducted without the intervention of an operator.

19. The method of claim 17, wherein the segmenting step is conducted without the intervention of an operator.

20. The method of claim 17, wherein the illuminating step further comprises illuminating the region of interest with light in at least one spectral band which penetrates to the papillary dermis and is re-emitted therefrom.

21. The method of claim 20, wherein the digital imaging step further comprises digitally imaging the region of interest with a digital camera.

22. The method of claim 20, wherein the illuminating step further comprises illuminating the region of interest with light in a near infrared spectral band.

23. The method of claim 17, further comprising suppressing specular reflections prior to the digital imaging step.

24. The method of claim 23, wherein the processor converts the digital signals of each of the digital images into values corrected for non-uniformities of illumination and of response prior to the segmenting step.

25. The method of claim 17, further comprising:

photographing the region of interest with a color camera to form color photographic slides; and

illuminating the color photographic slides with light in each spectral band;

wherein the digital imaging step comprises digitally imaging the illuminated color photographic slides of the region of interest with a digital camera.

26. The method of claim 17, wherein the segmenting step further comprises applying the segmentation mask to the digital images in the other spectral bands.

27. The method of claim 17, wherein the segmenting step comprises generating the mask at the shortest available wavelength.

28. The method of claim 17, wherein the illuminating step comprises illuminating the region of interest by light in at least one spectral band whose center is between about 400 to about 500 nanometers, and the segmenting step comprises generating the mask from a digital image at the spectral band between about 400 to about 500 nanometers.

29. The method of claim 19, wherein the segmenting step comprises generating the segmentation mask from a digital image by:

removing digital signals from the digital image which correspond to hair structures;

deriving a threshold from a multimodal histogram of intensity levels;

iteratively applying the threshold to the digital signals of the digital image; and

removing digital signals which correspond to small blob-like regions from the masked image.

30. The method of claim 19, wherein the segmenting step comprises generating the segmentation mask by comparing estimated values which are a function of textures within the digital images with a threshold.

31. The method of claim 30, further comprising generating the segmentation mask by comparing the estimated texture values to a threshold derived through statistical analysis of each digital image.

32. The method of claim 17, wherein the computing step comprises estimating at least one value which is a function of the texture of the region of interest determined by the segmentation mask.

33. The method of claim 32, wherein the computing step further comprises estimating values which are a function of the texture of the region of interest determined by the segmentation mask separately in each spectral band, based on the same segmentation mask.

34. The method of claim 32, wherein the computing step comprises estimating values which are statistical measures of local intensity variation in the digital images in each spectral band which are a function of texture.

35. The method of claim 17, wherein the computing step further comprises estimating a value which is a function of the asymmetry of the segmented image in each spectral band, for two principal axes of the segmented image.

36. The method of claim 35, wherein the computing step further comprises:

locating the principal axes by computing an orientation angle;

computing the intensity centroid;

rotating the digital image such that the principal axes are parallel to the image axes;

estimating asymmetry values for each principal axis based on the intensity centroid; and

summing the estimated asymmetry values for the two principal axes.

37. The method of claim 36, wherein the computing step further comprises computing the intensity moment with a binary intensity distribution.

38. The method of claim 17, wherein the computing step further comprises estimating at least one value which is a function of the blotchiness of the segmented digital image, the estimated blotchiness value being defined through statistical properties of the spatial distribution of topographic regions of the digital images at each spectral band.

39. The method of claim 38, wherein the computing step further comprises determining the centroids of topographic regions of the segmented digital image at each spectral band.

40. The method of claim 17, wherein the characterizing step comprises comparing a weighted combination of estimated values against a threshold value.

41. The method of claim 40, wherein the condition of the region of interest to be characterized is the presence of a melanoma and weight coefficients for each estimated value and the threshold value are selected to maximize specificity, under the constraint of a defined sensitivity to melanoma, on a representative set of training images.

42. The method of claim 17, where the characterization step is based on a non-linear combination of the estimated values.

43. The method of claim 17, where the characterization step is based on a linear combination of the estimated values.

44. The method of claim 17, where the characterization step is based on a sequential combination of applying a linear combination of the estimated values and a non-linear combination of estimated values.

45. A system for characterizing the condition of a region of interest of skin, comprising:

a source of illumination of light in at least three spectral bands;

a camera for acquiring digital images of the region of interest based on the light re-emitted from the illuminated region of interest at each of the spectral bands, the digital image comprising digital signals whose values are a function of the condition of the region of interest;

memory for storing the digital images provided by the camera;

a digital processor programmed to perform the steps of:

segmenting the digital images stored in memory by generating a single segmentation mask, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the at least three spectral bands;

estimating at least one value for each digital image at each spectral band which is a function of the texture of the portion of the region of interest determined by the segmentation mask;

characterizing the condition of the skin based on the estimated values; and

outputting the characterization of the region of interest.

46. The system of claim 45, further comprising means for suppressing specular reflections from the region of interest.

47. The system of claim 45, further comprising means for calibrating each digital image to provide correction for non-uniformities of illumination and response.

48. The system of claim 45, wherein the digital processor is coupled to the source of illumination and to the camera for controlling the intensity of illumination and exposure times, respectively.

49. The system of claim 45, wherein the processor applies the segmentation mask derived from the digital images at one spectral band to the digital images at the other spectral bands.

50. The system of the claim 45, where in the processor estimates values separately from digital images at each spectral band based on the segmentation mask.

51. The system of claim 49, wherein the processor compares a weighted combination of estimated values against a threshold value.

52. The system of claim 45, wherein the camera records monochromatic images and the illumination means comprises:

a tungsten halogen light source with feedback to stabilize the intensity in each wavelength band;

means for sequentially filtering the light; and

an optical fiber ring illuminator to distribute the filtered light.

53. The system of claim 45, further comprising a feedback loop for stabilizing the intensity of the light source by the processor.

54. The system of claim 45, wherein the filter means comprises a plurality of interference filters mounted on a wheel for stepping any filter into a position intercepting the light from the light source.

55. The system of claim 45, wherein at least one of the spectral bands has a center which is between about 400 to about 500 nanometers, and at least one other band centered elsewhere in the visible region.

56. The system of claim 55, wherein the set of interference filters includes a filter whose center lies in at least one spectral band in the near infrared range whose center lies between about 750 and 1000 nanometers.

57. The system of claim 50, wherein the camera is a single-chip, charge-coupled device and the control means comprises a digital computer including means for determining exposure times for the camera which maximize the signal-to-noise ratio in the image at each spectral band.

58. The system of claim 45, wherein:

the source of illumination provides broad-band ("white") light; and

the camera comprises multiple charge-coupled devices which detect light in a plurality of spectral bands between the near ultraviolet to near infrared.

59. The system of claim 45, wherein the processor estimates values which are statistical measures of local intensity variation in the digital images in each spectral band, which are a function of the texture of the region of interest.

60. The system of claim 45, wherein the processor estimates values based on the ratio of standard deviation of the areas of dermal papillae to their mean within the segmentation mask.

61. The system of claim 45, wherein the processor estimates values of the average and standard deviation of the thickness of rete ridges within the segmentation masks.

62. The system of claim 45, wherein the processor estimates at least one value which is a function of the asymmetry of the region of interest in each spectral band, for two principal axes of the segmented image by:

locating the principal axes by computing an orientation angle;

computing the intensity centroid;

rotating the digital image such that the principal axes are parallel to the image axes; and

estimating asymmetry values for each principal axis based on the intensity centroid; and

summing the estimated asymmetry values for the two principal axes.

63. The system of claim 45, wherein the processor further estimates at least one value which is a function of the blotchiness of the region of interest.

64. The system of claim 45, wherein the processor further estimates at least one value which is a function of the

irregularity of the border of the region of interest by estimating a value which is a statistical measure of the deviation of the border of the segmentation mask from the border of an ellipse of the same area, aspect ratio, and orientation as the segmentation mask.

65. The system of claim **45**, wherein the processor further estimates a value which is a function of the gradient at the border of the region of interest by estimating a statistical measure of the gradient values of the intensity of the digital images across the border of the segmented images, at each spectral band.

66. The system of claim **45**, wherein the processor characterizes the type of lesion as invasive or non-invasive.

67. The system of claim **45**, wherein the processor generates the segmentation mask from a digital image by:

removing digital signals from the digital image which correspond to hair structures;

deriving a threshold from a multimodal histogram of intensity levels;

iteratively applying the threshold to the digital signals of the digital image; and

removing digital signals which correspond to small blob-like regions from the masked image.

68. A system for characterizing the condition of a region of interest of skin, comprising:

a source of illumination of light in at least three spectral bands;

a camera for acquiring digital images of the region of interest based on the light re-emitted from the illuminated region of interest at each of the at least three spectral bands, the digital image comprising digital signals whose values are a function of the condition of the region of interest;

a memory for storing the digital images;

a digital processor including:

digital processing means for segmenting the digital images stored in memory and computing estimated values of parameters which are a function of the segmented images, wherein the digital images are segmented by generating a single segmentation mask, where the single segmentation mask is the segmentation mask having largest area of segmentation masks generated from each image in each of the at least three spectral bands;

digital processing means for automatically characterizing the condition of the tissue based on the estimated values; and

means for outputting the characterization of the region of interest.

69. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a segmentation mask defining the boundary of the region of interest from a digital image in any one of the at least three spectral bands;

computes at least one estimated value which is a statistical measure of the deviation of the boundary of the region of interest from the boundary of an ellipse of the same area, aspect ratio, and orientation as the segmentation mask;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin.

70. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a segmentation mask defining the boundary of the region of interest from a digital image in any one of the at least three spectral bands;

computes at least one estimated value of a statistical measure of the gradient values of the intensity of the digital images across the border of the segmented images;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin.

71. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a segmentation mask defining the boundary of the region of interest from a digital image in any one of the at least three spectral bands;

computes at least one estimated value based on the ratio of standard deviation of the areas of dermal papillae to their mean within the segmentation mask;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin.

72. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a segmentation mask defining the boundary of the region of interest from a digital image in any one of the at least three spectral bands;

computes at least one estimated value of the average and standard deviation of the thickness of rete ridges within the segmentation mask for a digital image of the region of interest determined by the segmentation mask;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin for a digital image of the region of interest determined by the segmentation mask.

73. A method of characterizing the condition of a region of interest of skin, wherein the absorption and scattering of light in different spectral bands by the region of interest is a function of the condition of the skin, the method comprising:

illuminating a portion of the skin including the region of interest by light in at least three spectral bands;

digitally imaging the portion of the skin including the region of interest at the at least three spectral bands with the light re-emitted by the portion of the skin to generate digital images comprising digital signals whose values are a function of the condition of the region of interest of the skin;

calibrating each pixel location in the digital image in each spectral band with respect to stored images of a white target material having known diffuse reflectance, each of the stored images being an average of a plurality of images acquired at each spectral band, while the material undergoes continual in-plane motion; and

providing the digital images to a processor, wherein the processor:

segments the digital images by generating a segmentation mask defining the boundary of the region of interest from a digital image in any one of the at least three spectral bands;

computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the region of interest determined by the segmentation mask;

characterizes the condition of the region of interest of the skin based on the estimated values; and

outputs the characterization of the condition of the region of interest of the skin.

* * * * *

EXHIBIT D

Maintenance Fee Receipts

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 37073 | ISTMT | DATE PRINTED 12/05/2011

MELA SCIENCES, INC.
50 SOUTH BUCKHOUT STREET, SUITE 1
IRVINGTON NY 10533

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,208,749	**$455.00**	**$0.00**	**09/09/04**	**09/032,450**	**03/27/01**	**02/27/98**	**04**	**YES**	**EOS-010**

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 37073 ISTMT DATE PRINTED 12/05/2011

MELA SCIENCES, INC.
50 SOUTH BUCKHOUT STREET, SUITE 1
IRVINGTON NY 10533

MAINTENANCE FEE STATEMENT

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,208,749	**$1,180.00**	**$0.00**	**04/14/08**	**09/032,450**	**03/27/01**	**02/27/98**	**08**	**YES**	**EOS-010**

EXHIBIT E

Filed Request for Certificate of Correction

PATENT
Attorney Docket No. EOS-010
(122463/211927)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Gutkowicz-Krusin *et al.*		
U.S. PATENT NO.:	6,208,749	SERIAL NO.:	09/032,450
ISSUE DATE:	March 27, 2001	GROUP NO.:	2623
FILING DATE:	February 27, 1998	EXAMINER:	Dastouri, Mehrdad
TITLE:	Systems and Methods for the Multispectral Imaging and Characterization of Skin Tissue		

ATTN: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Dear Sir:

The Assignee of record for the above-referenced patent, MELA Sciences, Inc., by virtue of an assignment from the inventors to Electro-Optical Sciences, Inc. (recorded on April 24, 1998 at Reel 009137, Frame 0244), and subsequent name change of Electro-Optical Sciences, Inc. to MELA Sciences, Inc. (recorded on May 7, 2010 at Reel 024351, Frame 0849), hereby requests that a Certificate of Correction be issued for U.S. Patent No. 6,208,749 under 35 U.S.C. § 255 and 37 C.F.R. § 1.323. The Assignee believes that the errors described below warrant issuance of a Certificate of Correction. Accordingly, the Assignee encloses a PTO Form 1050 to correct the errors in the above-identified patent.

The Assignee requests correction of errors in the Claims section of the above-identified patent. Specifically, in claim 17, the phrase "the at least tree spectral bands" should be deleted and replaced with the phrase "the at least three spectral bands."

The Assignee respectfully submits that the error in U.S. Patent 6,208,749 is due to an inadvertent clerical error, and does not introduce new matter or require reexamination of the patent. Accordingly, the Assignee respectfully requests that the Director issue a Certificate of

Correction for U.S. Patent No. 6,208,749 reflecting the correction as it appears on the enclosed PTO Form 1050.

Please charge our credit card in the amount of $100.00 covering the fee set forth in 37 C.F.R. § 1.20(a). The Director is hereby authorized to charge any deficiency in the fees filed to our Deposit Account No. 07-1700.

Respectfully submitted,

Date: December 19, 2011

Christopher W. Stamos, Reg. No. 35,370
Attorney for Applicants
Goodwin Procter LLP
Exchange Place
53 State Street
Boston, Massachusetts 02109

Tel. No.: (617) 570-1000
Fax No.: (617) 523-1231

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,208,749

APPLICATION NO.: 09/032,450

ISSUE DATE : March 27, 2001

INVENTOR(S) : Gutkowicz-Krusin et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 17, column 25, line 22, please delete "tree" and insert --three--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Christopher W. Stamos
Goodwin Procter LLP
Exchange Place
Boston, MA 02109

EXHIBIT F

Certificate of Approval Substantiating IRB Approval Date

WIRB®

Western Institutional Review Board®

Western International Review Board®

(360) 252-2500
FAX: (360) 252-2498
1-800-562-4789

3535 SEVENTH AVENUE, AVE SW, OLYMPIA, WA 98502-5010
P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Kenneth G. Gross, M.D.
Skin Surgery Medical Group, Inc.
5222 Balboa Avenue, 6th Floor
San Diego, CA 92117 USA

BOARD ACTION DATED: 05-02-2001
PANEL: 3
STUDY NR: 1027291
WIRB PRO NR: 20010367
INVEST NR: 5164

SPONSOR: Electro-Optical Sciences, Inc.
PROTOCOL NR: 20011
AMD. PRO. NR:
TITLE:
Patient Examination with MelaFind System Developed by Electro-Optical Sciences, Inc. (EOS)

APPROVAL INCLUDES:
Amendment to Protocol
Modification to Consent Form

All subjects currently enrolled in this study must sign the WIRB-approved consent form at their next regularly scheduled visit. Subjects enrolled in the future must sign the WIRB-approved consent form.

ALL CONDITIONS OF APPROVAL PREVIOUSLY ESTABLISHED BY WIRB FOR THIS RESEARCH PROJECT CONTINUE TO APPLY.

DISTRIBUTION OF COPIES

SPONSOR: Electro-Optical Sciences, Inc. **CONTACT:** Gabe Cruz
CRO:
INST:
SMO:
OTHER:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789

This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Ronald A. Jacobs for

William C. Jacobs, Chairman

MAY 09 2001

(Date)

EXHIBIT G

Letter Substantiating Date of Application for Product Approval

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

June 12, 2009

ELECTRO-OPTICAL SCIENCES, INC.
1 BRIDGE ST. SUITE 11
IRVINGTON, NEW YORK 10533
UNITED STATES
ATTN: JOSEPH V. GULFO

Dear JOSEPH GULFO:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA ORIGINAL. This PMA ORIGINAL has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P090012
Dated: 01-Jun-2009
Date Received: 09-Jun-2009
Device: MELAFIND

Any questions concerning this submission should be directed to the PMA staff at (240)276-4000. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted to the PMA Document Mail Center (DMC,HFZ-401) at the above letterhead address.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and the FDA Amendments Act of 2007 (FDAAA), authorizes FDA to collect user fees for certain types of PMA submissions. Please visit our website at http://www.fda.gov/cdrh/mdufma/index.html for more information regarding fees and FDA review goals.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf) accompany 510(k)/HDE/PMA applications. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" (http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html). According to the draft guidance, certain device applications to the FDA that are not related to clinical trials do not need the certification form.

We also remind you that Title III of FDAAA, section 515A(a)(2) of the Act, requires HDE applications, or PMA/PDP applications (or supplements to PMA/PDP applications) to include the following information: (1) a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and (2)the number of affected pediatric patients.

In future premarket submissions, we encourage you to provide (or continue to provide) an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopies Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see www.fda.gov/cdrh/elecsub.html.

Sincerely yours,

Pauline Fogarty
Consumer Safety Officer
Division of Surgical, Orthopedic and Restorative Devices
Office of Device Evaluation
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Electro-Optical Sciences, Inc. (EOS)
% Joseph V. Gulfo, M.D., M.B.A
President and CEO
1 Bridge Street, Suite #11
Irvington, New York 10533

AUG 18 2009

Re: P090012
Melafind

Dear Dr. Gulfo:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We inadvertently made an error in your Filing Letter which stated an incorrect July 9, 2009 Filing Date. The correct Filing date is June 9, 2009.

We hope that this incorrect Filing Date has not inconvenienced you. If you have any questions about this corrective action, please contact Atiq Chowdhury at (301) 796-6391.

Sincerely yours,

Mark N. Melkerson
Director
Division of Surgical, Orthopedic,
and Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Electro-Optical Sciences, Inc. (EOS)
% Joseph V. Gulfo, M.D., M.B.A
President and CEO
1 Bridge Street, Suite #11
Irvington, New York 10533

JUL 29 2009

Re: P090012
Melafind
Filed: July 9, 2009

Dear Dr. Gulfo:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is July 9, 2009, which is the date of CDRH receipt of the PMA.

We are also pleased to inform you that your application will receive expedited processing. Expedited review status was granted for the following reasons:

1. The MelaFind device described in your application does meet the criteria of a device intended to affect a condition that is life-threatening and is irreversibly debilitating. Early or better detection of melanoma has the potential to reduce both life altering surgeries and reduce mortality due to melanoma.

2. Use of the device has potential significant benefit to patients by: reducing unnecessary biopsies for suspicious melanomas, reducing potential biopsy adverse events such as scarring, infection, pain, and potentially improve the detection of early melanomas which will improve the survivability of patients diagnosed with melanoma.

3. The MelaFind device is a breakthrough technology in that it uses multiple wavelengths of light to produce multi-wavelength reflected optical signals for lesion diagnosis.

You are reminded that it is imperative that the information used to support an application for expedited review meet the requirements of valid scientific evidence (21 CFR 860.7). This evidence would generally be obtained from well-designed, -monitored, and -controlled clinical trials so that the true merit of the medical device might be evaluated as promptly and efficiently as possible. You are further advised that the granting of expedited review status does not guarantee that the application will ultimately be approved.

Please be advised that the decision to file the PMA does not imply that either an in-depth evaluation of the safety and effectiveness of the device has been performed or a decision about the approvability of the application has been made. Rather, it represents a decision by CDRH that the application is sufficiently complete to begin the substantive review process. Further review of your application may result in deficiencies which will be communicated to you.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may either 1) reasonably affect an evaluation of the safety or effectiveness of the device or 2) reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit clinical updates in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with the conditions set forth in your application and the applicable requirements of the Quality System Regulation (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301) 796-5815, or your District Office.

A meeting of The General and Plastic Surgery Devices Panel will be held at which your PMA will be reviewed. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA should be submitted in the form of a PMA amendment and be received by FDA at least 8 weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 8 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA supplement until a subsequent advisory panel meeting.

For your information, there is an industry representative on this FDA advisory panel whose name, address and telephone number you can obtain by contacting the Committee Management Staff at (240) 276-0450. CDRH believes that industry representatives will be better prepared to participate in panel discussions if they have been provided with at least a copy of the Summary of Safety and Effectiveness Data for review prior to the panel meeting. In accordance with 21 CFR 14.86(b), all panel members are subject to all rules and regulations adopted by FDA and the committee; therefore, even though the industry representatives usually are not given access to

trade secret and confidential, commercial information, they are bound to protect the confidentiality of documents that would be sent to them in preparation for panel review of a PMA. If you would like the industry representative to have access to any portion of your PMA, including the Summary of Safety and Effectiveness Data, please provide a copy to FDA for that purpose. Clearly identify the submission as a purged copy intended for review by the industry representative. Review of your PMA will not be prejudiced if you elect not to provide information for industry representative review.

All correspondence regarding this PMA should be submitted in six (6) copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions regarding this letter, please contact Atiq Chowdhury at (301) 796-6391.

Sincerely yours,

Mark N. Melkerson
Director
Division of Surgical, Orthopedic
and Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT H

Letter Substantiating PMA Approval Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room -WO66-G609
Silver Spring, MD 20993-0002

NOV - 1 2011

MELA Sciences, Inc.
% Joseph V. Gulfo, M.D., M.B.A
President and CEO
50 South Buckhout Street,
Suite 1,
Irving NY, 10533

Re: P090012
MelaFind®
Filed: June 9, 2009
Amended: September 24, October 27, 2009; March 29 (2), April 16 and 23, May 10 and 26, August 5, September 8 and 13, 2010; February 22, 2011; May 12, 2011; August 23 and 31; 2011; September 22, 2011; October 6, 2011 and November 1, 2011.
Procode: OYD

Dear Dr. Gulfo:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the MelaFind device.

MelaFind is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. MelaFind is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. MelaFind should NOT be used to confirm a clinical diagnosis of melanoma.

MelaFind is only for use by physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) who have also successfully completed a training program in the appropriate use of MelaFind.

The MelaFind result is one element of the overall clinical assessment. MelaFind positive lesions (which may include malignant melanoma, melanoma in situ, high grade dysplastic nevi and atypical melanocytic proliferation/hyperplasia) should be considered for biopsy; the biopsy decision of a MelaFind negative lesion should be based on the remainder of the entire clinical context. Lesions that are "non-evaluable" by MelaFind should be carefully re-evaluated for biopsy.

MelaFind is indicated only for use on lesions with a diameter between 2 mm and 22 mm, lesions that are accessible by the MelaFind imager, lesions that are sufficiently pigmented (i.e.

not for use on non-pigmented or skin-colored lesions), lesions that do not contain a scar or fibrosis consistent with previous trauma, lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions), lesions greater than 1 cm away from the eye, lesions which do not contain foreign matter, and lesions not on special anatomic sites (i.e., not for use on acral, palmar, plantar, mucosal, or subungual areas). MelaFind is not designed to detect pigmented non-melanoma skin cancers, so the dermatologist should rely on clinical experience to diagnose such lesions.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. You may continue commercial distribution of the device upon receipt of this letter.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" (please use this title even if the specified interval is more frequent than one year) and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS). Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. You must conduct a post approval study that will evaluate whether MelaFind increases the sensitivity of physicians in diagnosing melanomas and high-grade lesions, while the false positive rate of physicians is not substantially elevated.

2. The study will be a multi-center, single arm, observational, prospective study to gather data on relative sensitivity, among other study endpoints. Data to be collected includes: relative sensitivity comparing physicians' performance before and after using MelaFind as the primary study endpoint; real-world use of MelaFind, i.e., the patient characteristics including age, gender, race/ethnicity, and Fitzpatrick Skin Type, the number of lesions that were examined by MelaFind, the proportion of lesions that meet the labeled Indications For Use among all the lesions examined by MelaFind, the proportions of positive and negative findings of MelaFind among all of the lesions examined, the proportion of lesions that are un-evaluable by MelaFind, the proportion of lesions that are found to be un-evaluable for each user of MelaFind, the number of attempts with MelaFind that were performed for each lesion before a definitive reading resulted or the lesion was declared un-evaluable, and the impact of MelaFind use on the per physician biopsy rate for pigmented lesions; and an evaluation of safety and effectiveness of MelaFind, i.e., the proportion of biopsy from the lesions that MelaFind identifies as positive and the results of those biopsies, the proportion of biopsy among the "unreadable" lesions and the results of those biopsies, the proportion of biopsy from the lesions that MelaFind identifies as negative and the results of those biopsies, and the proportion of the biopsied lesions (from each of the above – MelaFind positive, MelaFind negative, and un-evaluable) returned as melanoma on pathology. This study must enroll 78 patients with one or more eligible and evaluable histologically-confirmed melanoma and/or high-grade lesion based on the null hypothesis that the relative sensitivity is less than or equal to 1.1. The study power will be at least 85%.

3. Patients with lesions evaluated with MelaFind during the enrollment period, but not biopsied at that time, will be followed at 1 year ±3 months and 2 years ±3 months. At least 50% of the study sites will be new (i.e., they did not participate in the MelaFind pivotal study). The study will enroll a mix of academic centers and private practices.

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

FDA would like to remind you that you are required to submit separate PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies for each study, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval

of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you;

however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this letter, please contact Atiq Chowdhury at 301-796-6391.

Sincerely yours,

Christy Foreman

Christy Foreman
Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

EXHIBIT I

Table of Significant Activities During the Review Period

MelaFind System Regulatory Summary

Description	Date	Originator
Letter to IDE Staff seeking confirmation that the MelaFind system does not require an approved Investigational Device Exemption (IDE) as a significant risk device and may obtain an approved IDE as a not significant risk device	8/17/2000	MELA[1]
Email requesting additional information in response to MELA's 8/17/00 inquiry	8/30/00	FDA
Email responding to FDA's 8/30/00 request for additional information	9/19/00	MELA
Email requesting additional information	9/20/00	FDA
Meeting with FDA, HCFA, and MELA to discuss various regulatory aspects of the MelaFind system, including FDA's confirmation that a PMA and advisory panel are required	2/13/01	MELA
IRB Approval for Protocol 20011 – Patient Examination with MelaFind System Developed by EOS	5/2/01	Western IRB (WIRB)
IRB Approval for Protocol 20012 – Non-invasive Breslow Thickness Measurement for Cutaneous Melanoma with MelaMeter	11/16/01	WIRB
Submission to address FDA's concern about the phototoxicity of the device for the agency's review of the not significant risk nature of the MelaFind system	3/18/02	MELA
Letter stating information from 8/17/00 and 3/18/02 submissions does not clearly indicate how the information from the MelaFind system will be used in the clinical investigation and therefore FDA cannot make a determination of whether the system poses a significant risk	4/1/02	FDA
Email responding to FDA's 4/1/02 letter explaining the two-phase clinical study plan: (1) a data collection phase and (2) the clinical trial phase	4/8/02	MELA
Email stating that the study is non-significant risk device trial	4/9/02	FDA

[1] MELA Sciences, Inc. was previously Electro-Optical Sciences, Inc. However, for purposes of this Regulatory Summary, we use "MELA" to refer to both.

Description	Date	Originator
PMA Shell for Modular Submission	11/7/02	MELA
PMA Modular Submission on manufacturing information	3/4/03	MELA
M020024/M2: Acceptance of PMA Modular Submission on manufacturing information; module is considered closed	7/17/03	FDA
Request for a meeting to discuss the clinical module (M3) of the PMA	8/15/03	MELA
Conference call to discuss possible claims and labeling for the MelaFind system	11/18/03	MELA
Submission of Protocol 20031 to FDA	11/24/03	MELA
Comments on Protocol 20031	6/1/04	FDA
Meeting to discuss Protocol 20031	6/4/04	MELA
Submission of Protocol 20031, revised to address FDA's comments during 6/4/04 meeting	6/21/04	MELA
Email with comments on Protocol 20031	8/5/04	FDA
Meeting to discuss Protocol 20031	8/6/04	MELA
Submission of Protocol 20031, revised to address FDA's comments in 8/5/04 email and 8/6/04 meeting	9/2/04	MELA
IRB Approval for Protocol 20031 – Evaluation of Pigmented Skin Lesions with MelaFind System [20031-A]	9/24/04	WIRB
Meeting to discuss Protocol 20031 and signing of the Binding Protocol Agreement under FD&C Act § 520(g)	10/20/04	MELA
Letter explaining the nature of the difficulties that were experienced with the MelaFind system during clinical trial 20031 and plans to address the issues prior to the start of pivotal trial 20061	6/13/05	MELA

Description	Date	Originator
M020024/M1: Acceptance of PMA Modular Submission on device design, pre-clinical data used to support the device design, software design, and certification to various international and national standards; module is considered closed. States when software algorithm is completed, company should submit additional information to this module or in the PMA.	7/16/05	FDA
Email stating the revised protocol 20061 "does not alter the pivotal study design" and the "changes do not alter the signed Study Agreement," *i.e.*, the Binding Protocol Agreement applied to Protocol 20061	1/4/06	FDA
IRB Approval for Protocol 20031-B – Pilot Roll-in Study for Protocol 20061: Evaluation of Pigmented Skin Lesions with MelaFind System	5/3/06	WIRB
Request for expedited review	8/10/06	MELA
Expedited Review granted	10/4/06	FDA
IRB Approval for Protocol 20061 – Evaluation of Pigmented Skin Lesions with MelaFind System	4/24/07	WIRB
First accrual for Protocol RCP2007-05 – Benign Pigmented Skin Lesions: Melanin Localization and Quantification with MelaFind System – study sponsored by L'Oreal and conducted in Austria and Switzerland and relied on in the PMA	9/26/07	L'Oreal
Submission of PMA for the MelaFind system	6/9/09	MELA
Acknowledgement of PMA P090012	6/12/09	FDA
Filing Letter for PMA P090012	7/29/09	FDA
Corrected Filing Letter for PMA P090012 – stating the correct Filing Date is June 9, 2009	8/18/09	FDA
Pre-Approval Inspection; 483 issued	8/10-13, 17-18, 21/09	FDA
Response to 483	9/2/09	MELA
FDA emails list of concerns related to the PMA	9/15/09	FDA

Description	Date	Originator
"100 Day" PMA Review Meeting	9/17/09	FDA
PMA Amendment P090012/A001 – submission of 9/17/09 meeting minutes and request that FDA immediately set a date for the panel meeting	9/24/09	MELA
Deficiency Letter (emailed to company on 10/13/09)	10/7/09	FDA
2nd response to 483	10/9/09	MELA
PMA Amendment P090012/A002- responding to Deficiency Letter	10/27/09	MELA
Establishment Inspection Report (EIR) issued to MELA for August 2009 inspection	11/2/09	FDA
FDA emails the company and states "it looks like we are heading toward a March date" for the panel meeting	11/23/09	FDA
Letter responding to MELA's 483 responses	12/11/09	FDA
Letter responding to FDA's 12/11/09 letter and providing an update to the 483 responses	1/8/10	MELA
Letter providing an update to MELA's 1/8/10 letter (483 responses)	3/1/10	MELA
Not Approvable Letter	3/10/10	FDA
PMA Amendment P090012/A003 and A004 [same PMA Amendment logged in twice by FDA] – requesting extension until 7/2/10 to submit a petition under FD&C Act § 515(d)(4) for review under § 515(g) of the Not Approvable Letter if company elects to treat not approvable letter as a PMA denial	3/29/10	MELA
Request for Supervisory Review under 21 CFR § 10.75 by CDRH Director Dr. Jeffrey Shuren of Not Approvable Letter	4/15/10	Goodwin Procter (on behalf of MELA)
PMA Amendment P090012/A005 – response to Not Approvable Letter	4/16/10	MELA
Letter providing an update to MELA's 1/8/10 and 3/1/10 letters (483 responses)	4/19/10	MELA

Description	Date	Originator
PMA Amendment P090012/A006 – withdrawal of P090012/A005 in order to facilitate the 4/27/10 meeting	4/23/10	MELA
Request that FDA hold in abeyance 4/15/10 request for supervisory review in order to facilitate meeting with review staff on 4/27/10	4/23/10	Goodwin Procter (on behalf of MELA)
Meeting to discuss Not Approvable Letter	4/27/10	MELA
PMA Amendment P090012/A007 – Response to Not Approvable Letter	5/10/10	MELA
PMA Amendment P090012/A008 – notifying FDA of name change from Electro-Optical Sciences, Inc. to MELA Sciences, Inc.	5/26/10	MELA
Federal Register notice announcing 8/26/10 panel meeting	6/24/10	FDA
Submission of Sponsor's draft panel package	7/13/10	MELA
Postponement of planned 8/26/10 panel meeting	7/16/10	FDA
PMA Amendment P090012/A009 – submission of data and analyses for Protocol 20063 Reader Study	8/5/10	MELA
Federal Register notice announcing 11/18/10 panel meeting	8/16/10	FDA
Meeting to facilitate preparations for November panel meeting	8/26/10	MELA
Teleconference to review final indications for use	9/3/10	MELA
PMA Amendment P090012/A010 – submission of revised claim	9/8/10	MELA
PMA Amendment P090012/A011 – submission of 8/26/10 meeting minutes and explanation of revised claim	9/13/10	MELA
Submission of Sponsor's revised panel package	9/27/10	MELA
Federal Register notice correcting 8/16/10 notice	10/5/10	FDA
Submission of Sponsor's final panel package	10/6/10	MELA
Agency's draft Executive Summary	10/18/10	FDA

Description	Date	Originator
Submission of comments on agency's draft Executive Summary and addendum to Sponsor's Executive Summary	10/20/10	MELA
Agency's revised Executive Summary	10/21/10	FDA
Submission of comments on agency's revised Executive Summary and revised addendum to Sponsor's Executive Summary	10/22/10	MELA
General and Plastic Surgery Devices Panel Meeting considering the PMA	11/18/10	FDA
Teleconference with FDA in which MELA requests a post Panel meeting	12/3/10	MELA
PMA Amendment - P090012/A012 - modifying the indications for use statement to define the intended users of the device as dermatologists	2/22/11	MELA
Submission of Citizen Petition asking that Commissioner Hamburg enforce the Oct. 20, 2004 Binding Protocol Agreement and require that MELA's PMA is reviewed fairly and consistently with FDA's laws and regulations	5/9/11	MELA
PMA Amendment P090012/A013 - for the draft MelaFind System User Training Program	5/12/11	MELA
During House Subcommittee for Oversight and Investigation hearing, CDRH Director Dr. Jeffrey Shuren states FDA staff incorrectly failed to send PMA to advisory panel	7/20/11	FDA
Letter identifying issues that warrant additional discussion between the company and FDA to reach an approvable decision	8/11/11	FDA
PMA Amendment P090012/A014 – Identifying areas of substantial disagreement with FDA's 8/11/11 letter	8/23/11	MELA
PMA Amendment P090012/A015 – Full response to FDA's 8/11/11 letter	8/31/11	MELA
Meeting to get PMA in approvable form	9/7/11	FDA

Description	Date	Originator
PMA Amendment P090012/A016 – Patient Labeling, User Guide, Package Insert, Training Program, Winter Clinical Reader Study, Slides from 9/7/11 meeting, Post Approval Study Protocol, References for tables provided in Package Insert	9/22/11	MELA
Approvable Letter	9/22/11	FDA
PMA Amendment P090012/A017 – In response to Approvable Letter: Revised Patient Labeling, Revised User Guide, Revised Package Insert, Answers to questions regarding Training Program and Revised Training Program elements, Responses to issues regarding the Post Approval Study and Revised Post Approval Study Protocol, Answers to questions regarding MelaFind software	10/6/11	MELA
PMA Amendment P090012/A018 - Final Patient Labeling, User Guide, Package Insert, and Summary of Safety and Effectiveness Data	11/1/11	MELA
PMA Approval	11/1/11	FDA